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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,786	05/11/2005	Elias Meezan	AEGIS1210	5393

28213 7590 06/29/2009

DLA PIPER LLP (US)
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
06/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No. 11/127,786	Applicant(s) MEEZAN ET AL.	
	Examiner JAMES H. ALSTRUM ACEVEDO	Art Unit 1616	

All Participants:

(1) *JAMES H. ALSTRUM ACEVEDO*.

(2) *Dr. Lisa A. Haile, Esq.*.

(3) _____.

(4) _____.

Status of Application: *Abandoned*

Date of Interview: *24 June 2009*

Time: *~5:05 pm EST*

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:
None

Claims discussed:
None

Prior art documents discussed:
None

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
Dr. Lisa Haile, Esq. confirmed that the instant application is abandoned.

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Applicant/Applicant's Representative Signature – if appropriate)

Notice of Abandonment	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *11/24/08*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☒ The reason(s) below:

Dr. Lisa Haile, Esq. confirmed that the instant application is abandoned.

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616

6/24/09

Interview Summary Attached

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

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Office Action Summary	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,9-12,18,23-24, 28,31-32,36-38, 40-44, 139-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,9-12,18,23,24,28,31,32,36-38,40-44 and 139-142* is/are rejected.

7)☒ Claim(s) *142* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

U.S. Patent and Trademark Office

DETAILED ACTION

Claims 1, 3, 7, 9-12, 18, 23-24, 28, 31-32, 36-38, 40-44, and 139-142 are pending. Applicants have newly cancelled claims 4-5, 8, 13, 17, 19-22, 25-27, 29-30, 33-35, 39 and 45-46. Claims 2 and 47-138 were previously cancelled. Applicants have amended claims 1, 3, 14-16, 23-24, 28, 31-32, and 40-42. Claims 139-142 are new. Receipt and consideration of Applicants' amended claim set and arguments/remarks submitted on August 25, 2007 are acknowledged. Any rejections or objections of record that have not been explicitly maintained herein are withdrawn per Applicants' claim amendments.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 25, 2008 has been entered.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 142 is objected to because of the following informalities: there is an extra space between the last word in said claim and the period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 140-142 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' new claims 140-142 recite a concentration of surfactant of about 0.25% (w) or 0.5% (w); however, Applicants' specification does not provide support for these concentration values. There is only explicit support for the values of 0.25% (w) and 0.5% (w), for example, in paragraphs 150 and 155, respectively. There is no support for these numerical values described modified by about. Applicants have not indicated where support may be found for surfactant concentrations of about 0.25% (w) or about 0.5% (w). If Applicants believe there is support for these concentration values, Applicants are kindly requested to provide the page and line numbers where support is found in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-32 and 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31-32 and 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: administering the drug composition. Independent claim 31 describes the intended target of the administration, but claim 31 never recites a step of administering the drug composition. The phrase "via ocular, nasal, intranasal, or intraperitoneal routes" is not a step. Thus, claim 31 and claims dependent therefrom omit the essential step of administering the composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.

3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7, 9-12, 18, 23-24, 28, 31-32, 36-38, 40-43, and 139-142 **are rejected** under 35 U.S.C. 103(a) as being unpatentable over Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130") in view of Young et al. (US 2003/0087820).[1]

Applicant Claims

Applicants claim (1) a surfactant composition comprising (a) exendin-4 and (b) at least one surfactant selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside, and tetradecyl maltoside; and (2) a method of administering a drug composition via ocular, nasal, intranasal, or intraperitoneal routes, comprising at least biologically active compound(s) and at least one surfactant, wherein the surfactant is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside, and tetradecyl maltoside and the drug is exendin-4; and (3)

a method of administering a drug composition via nasal, intranasal, or intraperitoneal routes, comprising at least biologically active compound(s) and at least one surfactant, wherein the surfactant is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside, and tetradecyl maltoside and the drug is exendin-4.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meezan '130 were set forth in the previous office action, and are restated herein. Meezan discloses in claims 1-5 and 8-10:

1. A method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

2. The method of claim **1**, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

3. The method of claim **1**, wherein the alkyl has from 9 to 24 carbons.

4. The method of claim **3**, wherein the alkyl has from 9 to 14 carbon atoms.

5. The method of claim **4**, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

8. The method of claim **1**, wherein the compound is a protein or a peptide.

9. The method of claim **8**, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

10. The method of claim **8**, and further comprising administering a protease or peptidase inhibitor.

Meezan discloses that preferred **glycosides include maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12, or 14 carbon atoms** (col. 6, lines 46-51). Compounds which can exhibit an increased absorption by Meezan's invented method include **peptide hormones (e.g. insulin, calcitonin, enkephalins, glucagon), hypoglycemic agents (e.g. tolbutamide and glyburide**), and agents which are poorly absorbed by enteric routes (e.g. friseofulvin) (col. 5, lines 17-32).

[1] New claims 139-142 have been appended to this rejection.

The claimed properties of the claimed surfactants are inherent to these compounds. Wherein the prior art discloses the same compounds, these must have the same properties, because a compound and its properties may not be separated.

Young teaches exendin and exendin agonist formulations suitable for any known route of administration, such as intranasal administration. Exendin-4 is a known naturally occurring hormonal peptide that is known to have a longer duration of effect than GLP-1, and similar to GLP-1 has been demonstrated to lower glucose levels in diabetic mice (title; abstract; Figure 10; [0047]; [0224]-[0227]; [0231]-[0239]; Examples 1-7 and Example 9).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meezan '130 lacks the teaching of a composition comprising exendin-4. This deficiency is cured by the teachings of Young.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Meezan '130 and Young, because Meezan teaches that the invented compositions comprising absorption enhancers may comprise peptidic hormones as the active agent (i.e. insulin or glucagon) and Young teaches compositions comprising a peptidic hormone (e.g. exendins, such as exendin-4). It would have been prima facie obvious to modify Meezan's compositions to utilize exendin-4 in addition to insulin or in lieu of insulin, because exendin is known to be

suitable for lowering blood glucose in diabetic mice, which is an analogous function accomplished by the administration of insulin. The functional similarity in the therapeutic effect of insulin and exendin-4 with regards to the lowering of blood glucose would provide the ordinary skilled artisan with motivation to modify Meezan's compositions and would also have provided a reasonable expectation of success upon addition of exendin-4 to or in place of insulin in Meezan's compositions. Regarding the stabilizing, high NOAEL, antibacterial, and AUC properties recited in Applicants' compositions, these properties are attributed to the alkyl glycoside surfactants, including the very same alkyl glycoside surfactants utilized in Meezan's formulations. Thus, Meezan's formulations necessarily would exhibit the same properties, because a compound and its properties are inseparable regardless of whether the prior art recognized the presence of said properties. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 8/25/08 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by attacking the references individually and arguing that (1) the reference is allegedly improper because Young does not teach the ocular route of administration; (2) there is allegedly no motivation to combine the cited references; (3) the cited references allegedly fail to disclose any guidelines as to amount of peptide or protein that may be administered or amounts of

alkylglycoside to be utilized with exendin-4; (4) Meezan is allegedly improperly relied upon because Meezan does not disclose anticipatory compositions comprising exendin-4 in combination with the specific alkyl glucosides recited in Applicants' claims; (5) there is allegedly no reasonable expectation of success; and (6) Meezan is allegedly improper because Meezan does not teach intranasal administration alone using the specific alkyl glycosides in the concentrations recited in Applicants' new claims; (7) Applicants' claims allegedly constitute a subgenus of the genus disclosed in Meezan comprising a vast number of combinations of alkyl glycosides, concentrations, and drugs; and (8) exendin-4 was not a known therapeutic at the time of Meezan.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments (1) and (6)-(8) against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, regarding (8), the standard for the determination of obviousness is based on what was known at the time of Applicants' invention and is not limited to what was known at the time of an older cited reference.

Regarding (2), Applicants merely assert that there is no motivation to combine the cited references. Applicants fail to provide any specific and substantive reasons explaining their position that an ordinary skilled artisan would allegedly by unmotivated to combine the cited prior art teachings. In fact, there is a clear motivation to combine the cited teachings: both insulin (Meezan) and exendin-4 (Young) are art recognized therapeutics that have the same effect of lowering blood sugar levels. It is generally

considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). Furthermore, it would also be obvious to substitute insulin for exendin-4, because both insulin and exendin-4 result in the lowering of blood sugar levels and are both protein therapeutic drugs. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating exendin-4 compositions comprising alkyl glycosides for administration across mucosal tissue, such as ocular, nasal, and pulmonary tissues.

Regarding (3), Applicants are mistaken. Meezan explicitly teaches that suitable amounts of alkyl glycosides may range from 0.01-1% w/w. See Meezan's claim 2, for example. Meezan's examples utilize tetradecyl maltoside, decyl maltoside, dodecyl sucrose, tridecyl maltoside (e.g. col. 11, line 1 through col. 12, line 35). In col. 6, lines 46-51, Meezan explicitly indicates that Applicants' alkyl glycosides are preferred alkyl glycosides. Concerning the amount of active agent, as Applicants are well aware, the amount of drug that is suitable for a patient is variable and depends on a patient's age, gender, overall health, weight, etc. and is easily determinable by the ordinary skilled artisan (Meezan: col. 7, lines 13-18). It is also noted that Applicants' claims do not specify any particular amount of therapeutic agent.

Regarding (4), Applicants are reminded that the instant rejection is based on §103(a) (i.e. "obviousness") and not §102 (i.e. "anticipation"). Thus, the fact that Meezan does not anticipate Applicants' claims is not dispositive as to whether the instant

rejection is proper or not. The rejection is proper for the reasons of record and further articulated above.

Regarding (5), Applicants allege that there is no reasonable expectation of success, because the pharmaceutical arts are unpredictable; there are variations of absorption across different types of epithelial cells; exendin-4 allegedly has unspecified characteristics that would implicitly create a reasonable expectation of failure; and the concentrations and properties of the alkyl glycosides recited in Applicants' claims necessary to increase absorption across nasal mucosa allegedly render an expectation of success unreasonable. This is unpersuasive, because Meezan explicitly teaches that the invented alkyl glycosides (the same alkyl glycosides recited in Applicants' claims) are suitable to increase absorption when administered via the ocular, nasal, nasolacrimal, and inhalation routes. The burden is upon Applicants to provide objective evidence regarding specific properties of exendin-4 that would support an allegation of an expectation of failure. Unlike insulin, calcitonin, glucagon, and other protein therapeutics that are taught by Meezan as being administrable via the ocular, nasal, nasolacrimal, and inhalation routes, Applicants have cited no specific property of exendin-4, which would lead the ordinary skilled artisan to conclude that there would be no reasonable expectation of success. Applicants' arguments amount to nothing more than mere attorney argument, unsupported by objective evidence. Thus, the Examiner concludes that the cited prior art teachings do provide a reasonable expectation of success.

Regarding (7) and the implied allegation that the teachings of Meezan are so vast as to render the instant claims a non-obvious sub-genus, the Examiner respectfully disagrees. Meezan does not disclose a vast number of alkyl glycosides as alleged, but

rather directs the ordinary skilled artisan to select an alkyl glycoside from one of 12 possibilities (see col. 6, lines 46-49). Twelve possible choices for an alkyl glycoside is not a vast number. Furthermore, Meezan exemplifies compositions comprising 4 of the 5 specific alkyl glycosides in the compositions and methods claimed by Applicants. Meezan also discloses a very specific amount of alkyl glycoside, namely a range of 0.01-1% w/w. A concentration range covering a difference of approximately 1 weight percent is clearly not a vast range. Meezan's teachings clearly are focus on proteinic therapeutic agents. Meezan's teachings as modified by Young do not encompass a vast number of possible therapeutic agents. Applicants' have not alleged any unexpected results or provided evidence that compositions comprising the specific alkyl glycosides taught by Meezan, in the amounts taught by Meezan, and as modified by Young to comprise exendin-4 would exhibit any unexpected properties. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claim 44 **remains rejected** under 35 U.S.C. 103(a) as being unpatentable over Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130") in view of Young et al. (US 2003/0087820), as applied above to claims 1, 3, 7, 9-12, 18, 23-24, 28, 31-32, 36-38, 40-43, and 139-142 and further in view of Crotts (US 2003/0017203; already of record).

Applicant Claims

Applicants claim a composition as described above which further comprises an enteric coating.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meezan and Young have been set forth above in the instant office action. Crotts teaches an oral peptide pharmaceutical dosage form for the oral delivery of a peptide composition that includes an absorption enhancer effective to promote the bioavailability of the peptide and an **enteric coating** (title; abstract; claims 1 and 16-17). Crotts teaches that the invention is suitable for patients who suffer from disorders or diseases that are treatable by administration of a peptide [0013]. Suitable enteric coatings are described in [0034]-[0036]. Crotts focuses on the administration of calcitonin ([0013]; claims).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meezan '130 lacks the teaching of a composition further comprising an enteric coating. This deficiency is cured by the teachings of Crotts.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Meezan/Young and Crotts, because Meezan/Young teach compositions comprising absorption enhancers and the same active

agent (i.e. calcitonin) taught as being the active peptide in Crotts compositions. An ordinary skilled artisan would have been motivated to combine the teachings of Meezan/Young and Crotts because Crotts teaches that the invented compositions comprise absorption enhancers and can comprise any peptide that is useful in the treatment of a disease or condition, such as calcitonin, and Meezan/Young teaches calcitonin compositions comprising alkyl glycoside absorption enhancers. An ordinary skilled artisan would have been further motivated to combine the teachings of Meezan and Crotts, because the presence of an enteric coating in Crotts compositions when combined with the teachings of Meezan/Young would enable the oral administration of calcitonin, exendin-4, and other active peptide formulations. Because the enteric coating of Crotts compositions would be expected to prevent the degradation of peptide active agents, such as calcitonin, exendin-4, or insulin, an ordinary skilled artisan would have had a reasonable expectation of success upon modification of the teachings of Meezan with the teachings of Crotts.

Response to Arguments

Applicant's arguments filed 8/25/08 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by reiterating the arguments traversing the previous rejection under §103. The Office's rebuttal of these arguments is herein incorporated by reference. Applicants' also have argued that Ladner et al. also fail to cure the deficiencies of the '040 patent. The Examiner does not understand Applicants' additional argument, because the instant rejection is not based on any reference to a "Ladner et al." or a '040 patent. See the statement of rejection supra.

This is found unpersuasive, because the claim 44 does not recite any particular required composition stability. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 141 be found allowable, claim 142 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-

type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 7, 23, 31, and 40-43 **remain rejected** on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (USPN '130) in view of Young et al. (US 2003/0087820) for the reasons of record restated below.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. It is noted that the cited claims of USPN '130 are drawn to methods of increasing absorption of a compound into the circulatory system comprising administration of a compound and an absorption increasing amount of a suitable non-toxic, nonionic alkyl glycoside. It is noted that dependent claims 8-10 of USPN '130 specify that the compound in the composition is a protein or peptide, such as insulin and glucagon, and/or method further comprises the administration of a protease or peptidase inhibitor. The main difference between the claims of the instant application and the claims of USPN '130 do not recite

that the compositions comprise exendin-4. Nonetheless, the claims of USPN "130 indicate that the claimed compositions may comprise peptidic hormones, such as insulin and glucagon. The teachings of Young cure this deficiency and have been set forth above.

Young clearly teaches that exendin-4 has been shown to reduce blood glucose levels in diabetic mice as well as healthy human volunteers. Lowering blood glucose levels is also a well known effect of insulin. Thus, it would have been prima facie obvious to an ordinary skilled artisan to add exendin-4 to the compositions utilized in Meezan's claimed method. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). The compositions utilized in the claimed methods of USPN '130 obviate the cited composition claims of the instant application. Regarding the claimed properties indicated as being due to the presence of alkyl glycoside surfactants in Applicants' claims, these properties would necessarily be present in the compositions utilized in the claimed methods of USPN '130, because these compositions comprise the same alkyl glycoside surfactants indicated by Applicants as providing the stabilization, anti-microbial, and high NOAEL properties. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that claims of the instant application are *prima facie* obvious over claims 1-5 and 8-10 of USPN '130.

Response to Arguments

Applicant's arguments filed 8/25/08 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by reiterating the arguments traversing the first rejection under §103 supra. The Office's rebuttal of these arguments is herein incorporated by reference. Applicants' also have argued that Young fails to cure the deficiencies of the '040 patent. The Examiner does not understand Applicants' additional argument, because the instant rejection is not based on any reference to a '040 patent. See the statement of rejection supra. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

The provisional rejection of claims 1, 11, 31, and 43 **remain rejected** on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825) **is maintained** for the reasons of record, which have been restated herein.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims are substantially overlapping in scope and mutually obvious. Independent claim 1 of copending '825 claims a method of administering an alkyl saccharide composition comprising administering at least one alkyl saccharide having an alkyl chain length from 12 to about 14 carbon atoms and at least one saccharide moiety with antibacterial activity, at least one therapeutic agent and at least one enhancing agent. The term alkyl saccharide reads on alkyl glycoside. Independent

claim 1 of the instant application claims a surfactant composition comprising at least one alkyl glycoside and/or at least one saccharide alkyl ester that when admixed with a drug stabilizes the biological activity and increases the bioavailability of the drug. Saccharide alky ester reads on enhancer. It is obvious from the wording of claim 1 of the instant application that the surfactants are intended to be mixed with a drug. Therefore, claim 1 of the instant application is obviated by the composition utilized in claim 1 of copending '825. Independent claim 31 of the instant application claims a method of administering a drug composition comprising a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alky has from about 10 to about 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug. The term "delivered" reads on administering. Both claims 11 and 43 state that the surfactant composition of the instant application is formulated for mucosal delivery. Mucosal delivery reads on "transmucosal delivery." In conclusion, an ordinary skilled artisan would have concluded that claims 1, 8, 11, 31, and 43 of the instant application are prima facie obvious over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants have not traversed the instant rejection, but rather have requested that the instant rejection be held in abeyance. Rejections cannot be held in abeyance; thus,

the rejection is maintained and Applicants' comments are interpreted as Applicants' agreement that the instant rejection is proper.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Katzung, B., (*Basic and Clinical Pharmacology, 7th edition*, Appleton & Lange: Stamford, Connecticut, 1998, pp 34-49) is relevant, because it establishes what was well known regarding pharmacokinetics/pharmacodynamics and that the bioavailability of intravenous administration is 100% and the bioavailability of intramuscular administration is less than or equal to 100% (See Table 3-3).

Claims 1, 3, 7, 9-12, 18, 23-24, 28, 31-32, 36-38, 40-44, and 139-142 are rejected. Claim 142 is objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H Alstrum-Acevedo/
Patent Examiner, Art Unit 1616
Technology Center 1600

Notice of References Cited	Application/Control No. 11/127,786	Applicant(s)/Patent Under Reexamination MEEZAN ET AL.	
	Examiner JAMES H. ALSTRUM	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	D	US-			
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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Katzung, B., "Basic and Clinical Pharmacology, 7th edition", Appleton & Lange: Stamford, Connecticut, 1998, pp 34-49.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11127786	MEEZAN ET AL.
	Examiner	Art Unit
	JAMES H ALSTRUM ACEVEDO	1616

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
Discussed the AUC limitations in claims 24 and 28 with Dr. Johnny Railey III (RQAS) and Dr. Jake Minh Vu (1617), who is a pharmacist by training, and we concluded that these claims were enabled.	11/17/08 and 11/18/08	JHAA
PALM & WEST Searches	11/19/08	JHAA

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

Inventor Information for 11/127786

Inventor Name	City	State/Country
MEEZAN, ELIAS	BIRMINGHAM	ALABAMA
PILLION, DENNIS J.	HOOVER	ALABAMA
MAGGIO, EDWARD T.	SAN DIEGO	CALIFORNIA

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign D

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Term: (((((((Dennis near4 Pillion) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210) AND @pd>20080303) AND @pd>20080903)

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L3	(((((((Dennis near4 Pillion) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210) AND @pd>20080303) AND @pd>20080903)	0	L3
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L1	(((((((Edward near4 Maggio) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210) AND @pd>20080303) AND @pd>20080903)	4	L1

END OF SEARCH HISTORY

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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	11/127,786
Filing Date	May 11, 2005
First Named Inventor	Elias Meezan
Art Unit	1616
Examiner Name	J.H. Alstrum Acevedo
Attorney Docket Number	AEGIS1210

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **Submission required under 37 CFR 1.114**

a. ☐ Previously submitted
   i. ☐ Consider the amendment(s)/reply under 37 C.F.R. 1.116 previously filed on _____
   (Any unentered amendment(s) referred to above will be entered).
   ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   iii. ☐ Other _____

b. ☒ Enclosed
   i. ☒ Supp. Response to Final Office Action (16 pgs.)
   ii. ☐ Declaration under 37 C.F.R. §1.132 (__ pgs.)
   iii. ☐ Information Disclosure Statement (IDS)
   iv. ☐ Sequence Listing in .txt Format

2. **Miscellaneous**

a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) **required**)

b. ☐ Other _____

3. **Fees** The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

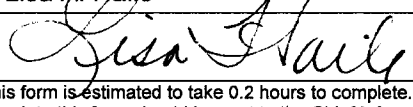
a. ☒ The Director is hereby authorized to charge the total amount of $635.00 to Deposit Account No. 07-1896. Additionally, the director is further authorized to charge any additional fees, or credit any overpayments, to Deposit Account No. 07-1896.

   i. ☒ RCE fee required under 37 CFR 1.17(e) ($405.00)
   ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17) ($230.00)
   iii. ☐ Other _____

b. ☐ Check number __ in the total amount of $_____ is enclosed
c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print /Type)	Lisa A. Haile	*Registration No. (Attorney/Agent)*	38,347
Signature		*Date*	August 25, 2008

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND Fees and Completed Forms to the following address: **Mail Stop PETITION, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL RESPONSE TO THE FINAL OFFICE ACTION

Sir:

Responsive to the Office Communication mailed August 1, 2008 and the Final Office Action mailed March 24, 2008, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Amendments to the Claims

Please amend claims 1, 3, 14-16, 18, 23-24, 28, 31-32 and 40-42 as provided below.

Please cancel claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35, 39, 45 and 46 without prejudice or disclaimer.

Please add new claims 139-142.

Listing of Claims:

1. (Currently amended) A surfactant composition comprising at least one alkyl glycoside or at least one saccharide alkyl ester admixed with a drug, wherein the surfactant maintains the biological activity and increases the bioavailability~~,~~ of the drug, wherein the drug is exendin-4 and the surfactant is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

2. (Canceled)

3. (Currently amended) The composition of claim 1, wherein the ~~surfactant~~ composition has a ~~high~~ no observable adverse effect level (NOAEL) that is acceptable for daily intake.

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. (Original) The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. (Canceled)

9. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. (Original) The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. (Previously presented) The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system of a subject.

13. (Canceled)

14. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 20% (w/~~v~~).

15. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 5% (w/~~v~~).

16. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 2% (w/~~v~~).

17. (Canceled)

18. (Currently amended) The composition of claim 1~~7~~, wherein the composition has a pH less than 8.0.

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Currently amended) The ~~therapeutic~~ composition according to claim 1~~7~~, wherein the composition is formulated for mucosal administration to a subject.

24. (Currently amended) The ~~therapeutic~~ composition according to claim 1~~7~~, wherein administration to a subject yields enhanced mucosal delivery of said biologically active compound(s) ~~comprising:~~ characterized by

~~a) a peak concentration (C_{max}) of the biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of the subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;~~

~~b)~~ an area under concentration curve (AUC) of the biologically active compound(s) ~~in the central nervous system (CNS) tissue or fluid or~~ in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in ~~CNS or~~ blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject~~; or~~

~~c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.~~

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Currently amended) The ~~therapeutic~~ composition of claim ~~17~~, wherein the composition following mucosal administration to a subject yields an area under concentration curve (AUC) of the biologically active compound(s) ~~in the CNS tissue or fluid or~~ in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in the ~~CNS or~~ blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. (Canceled)

30. (Canceled)

31. (Currently amended) A method of administering a drug composition via ocular, nasal, intranasal or intraperitoneal routes comprising a surfactant that increases the bioavailability of the drug having at least one alkyl glycoside ~~or saccharide alkyl ester~~ mixed with at least one drug and delivered to a subject, wherein the drug is exendin-4 and the alkyl has from about 10 to 24 carbon atoms and is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside~~, and the surfactant increases the bioavailability of the drug wherein the drug is exendin-4~~.

32. (Currently amended) The method of claim 31, wherein the ~~surfactant~~ composition has a ~~high~~ no observable adverse effect level (NOAEL) that is acceptable for daily intake.

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Previously presented) The method of claim 31, wherein the surfactant reduces variance in bioavailability from patient to patient.

37. (Previously presented) The method of claim 31, wherein the composition does not enter the hepatic portal blood system of a subject.

38. (Previously presented) The method of claim 31, wherein the composition has a pH less than 8.0.

39. (Canceled)

40. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 20% (w/~~v~~).

41. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 5% (w/~~v~~).

42. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 2% (w/~~v~~).

43. (Original) The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. (Previously presented) The composition of claim 1, wherein the composition further comprises an enteric coating.

45. (Canceled)

46. (Canceled)

47. – 138. (Canceled)

139. (New) A method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

140. (New) The method of claim 139, wherein the surfactant is at a concentration of about 0.25% (w).

141. (New) The method of claim 139, wherein the surfactant is at a concentration of about 0.5% (w).

142. (New) A method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is at a concentration of about 0.5% (w) and is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside.

REMARKS

The remarks are responsive to the Office Communication mailed August 1, 2008 and the Final Office Action mailed March 24, 2008. In the present amendment, claims 1, 3, 14-16, 18, 23-24, 28, 31-32 and 40-42 have been amended; claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35, 39, 45 and 46 have been canceled without prejudice or disclaimer; and new claims 139-142 have been added. The amendments add no new matter as the claim language is fully supported by the specification and original claims.

Rejections under 35 U.S.C. §112, First Paragraph (written description)

Claims 17-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

It is well-established that an objective standard for determining compliance with the written description requirement is, whether the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see, *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed (see, *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and MPEP §2163.04).

The Office Action alleges the specification does not describe any compositions characterized by stability of the biologically active compound for at least 6 months at temperatures from about 4°C to 25°C in sufficient detail to demonstrate possession at the time the instant application was filed. Additionally, the Office Action further alleges that the specification lacks data or written support to demonstrate that Applicants were in possession of compositions characterized by peak concentration values (C_{max}), area under the curve (AUC) and time to maximal concentration (t_{max}) as recited in claims 23-30 because there allegedly is no such data presented in the specification or figures.

Without acquiescing to the reasoning presented in the Office Action, and in order to expedite prosecution of the instant application, Applicants have canceled claims 17, 19-22, 25-27, 29-30, 33-35 and 39, without prejudice or disclaimer rendering the rejection moot as to such claims. Additionally, claims 18, 23, 24 and 28 have been amended to depend from claim 1 which does not recite the rejected stability characteristics (*e.g.,* "maintains the biological activity of the drug, for at least about 6 months from about 4°C to 25°C") rendering the rejection moot as to such claims. Further, claims 45 and 46 depend from claim 1 rendering the rejection moot as to such claims. With regard to amended claims 24 and 28, the claims have been amended by deleting reference to C_{max}, t_{max} and "CNS tissue" to clarify that the AUC is of blood plasma. Determination of bioavailability is discussed in the specification as filed, for example, in paragraphs [0074] and [0075] and Applicants respectfully submit that AUC may be readily extrapolated from Figure 1 which is discussed in Example 2 because bioavailability is directly derived from a simple comparison of proportions of AUC for an intravenous and oral dosage.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 14-16, 20-22 and 40-42 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office Action alleges that the specification does not support concentrations of surfactant in units of weight/volume (w/v), but rather supports concentrations expressed as weight percentages as shown in paragraphs 70 and 88. Without acquiescing to the reasoning presented in the Office Action, and in order to expedite prosecution of the instant application, Applicants have canceled claims 20-22 without prejudice or disclaimer rendering the rejection moot as to such claims. Additionally, Applicants have amended claims 14-16 and 40-42 to reflect concentrations in weight percentages as suggested in the Office Action.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph (enablement)

Claims 31-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims. Claims 33-35 and 39 have been canceled without prejudice or disclaimer rendering the rejection moot as to such claims.

The Office Action alleges that while exendin-4 is enabled, it is allegedly only enabled for methods of administering exendin-4 in combination with an alkyl glycoside selected from the group consisting of dodecyl sucrose (DDS), dodecyl maltoside (DDM), tridecyl maltoside (TDM) and tridecyl maltoside (TriDM) via ocular, nasal, intranasal, or intraperitoneal administration (see the Office Action, page 10 last paragraph through page 11, first and second paragraphs).

Without acquiescing to the reasoning presented in the Office Action and in order to expedite prosecution of the present application, Applicants have amended claim 31 to recite as follows:

> 31. A method of administering a drug composition via ocular, nasal, intranasal or intraperitoneal routes comprising a surfactant that increases the bioavailability of the drug having at least one alkyl glycoside mixed with at least one drug and delivered to a subject, wherein the drug is exendin-4 and the alkyl has from about 10 to 24 carbon atoms and is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claims 3-6 and 32-35 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

Specifically, the Office Action also alleges that claims 3-6 and 32-35 contain the indefinite term "high". Without acquiescing to the reasoning presented in the Office Action and in order to expedite prosecution of the instant application, Applicants have canceled claims 4-6 and 33-35 without prejudice or disclaimer. Additionally, Applicants have amended claims 3 and 32 to recite that the "composition has a no observable adverse effect level (NOAEL) that is acceptable for daily intake". As such, the claim no longer recites the term "high".

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1, 3-43 and 45-46 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter "the '130 Patent") in view of Young et al. (US 2003/0087820). Applicants respectfully traverse the rejection as it applies to the pending claims. Claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35 and 39 have been canceled rendering the rejection moot as to such claims.

The recent U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the

general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness with regard to the amended claims, because there would be no motivation for one of skill in the art to combine the references. The Office Action concedes that the '130 Patent fails to specifically teach compositions including exendin-4. To cure the deficiency, the Office Action utilizes Young et al. and alleges that Young et al. teaches compositions comprising exendin-4 for any known route of administration, such as intranasal administration. Applicants respectfully disagree and point out that Young et al. fails to teach administration via the ocular route as presently recited in claim 31. Additionally, the compositions disclosed in Young et al. are formulated for extended release and utilize an ionic surfactant, such as alkali polyether alcohol sulfates or sulfonates (*e.g.* Triton) or a surfactant of polysorbate 80 or other non-ionic detergent such as Tween. Applicants respectfully submit that there would be no motivation for one of skill in the art to combine the references to practice the inventions presently claimed which includes the proviso that the surfactant maintains the biological activity and increases the bioavailability of the drug. Applicants respectfully submit that neither reference discloses maintaining the biological activity and increasing the bioavailability of the exendin-4 and therefore one of skill in the art would not have been motivated to utilize exendin-4 in combination with the claimed surfactants to achieve the claimed characteristics.

Even if one were to modify the '130 Patent, there is no *prima facie* case of obviousness as to the amended claims, because there would be no expectation of successfully practicing the claimed invention. None of the cited references provide sufficient guidance to ensure a reasonable expectation of success of practicing the claimed invention given the unpredictability in the art.

The cited references fail to disclose any formulations including exendin-4 in combination with an alkylglycoside surfactant, especially any of the surfactants claimed. Additionally, the cited references fail to disclose any guidelines as to amounts of peptide or protein that may be

used or amounts of alkylglycoside to be utilized with exendin-4. Without such teachings, Applicants respectfully submit that there could have been no reasonable expectation of success in carrying out the claimed invention because the prior art fails to sufficiently teach how one of skill in the art would go about practicing the claimed invention.

With regard to new claims 139-142, Applicants respectfully submit that the subject matter of such claims is not obvious over the '130 Patent. As recited, new claim 139 is directed to a "method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside." Additionally, claims 140 and 141 recite specific concentrations of alkyl glycoside to be utilized, while new claim 142 is directed to intranasal administration of exendin-4 in combination with dodecyl sucrose, dodecyl maltoside or tridecyl maltoside at a concentration of 0.5%.

Applicants respectfully submit that the '130 Patent fails to disclose intranasal administration of exendin-4 in combination with dodecyl sucrose, dodecyl maltoside, tridecyl maltoside or tetradecyl maltoside at the recited concentrations, 0.5% (w) or 0.25% (w). While the '130 Patent discloses broad concentration ranges of alkyl glycosides and includes examples utilizing ocular administration of insulin, the '130 Patent fails to teach intranasal administration alone using the specific alkyl glycosides and concentrations recited in the new claims as well as increasing the stability and bioavailability of the drug at such concentrations. Applicants submit that without such teachings, the claimed invention would not have been obvious to one of skill in the art because there could be no reasonable expectation of successfully practicing the claimed invention. Given the unpredictability inherent in drug formulation combined with the variations of absorption across different types of epithelial cells, as well as the individual characteristics of exendin-4 and specific alkyl glycosides at specific concentrations, the formulation for intranasal administration including exendin-4 in combination with specific alkyl glycosides at specific

concentrations sufficient to increase stability and bioavailability of exendin-4 would not have been obvious to one of skill in the art.

Additionally, Applicants respectfully submit that the present claims encompass a defined subgenus of that disclosed and claimed in the '130 Patent. The fact that a claimed species or subgenus is encompassed by a prior art genus does not establish a *prima facie* case of obviousness (see, *In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). Applicants respectfully submit that the genus disclosed in the '130 Patent is broad and encompasses vast combinations of alkyl glycosides, concentrations, and drugs. Additionally, the '130 Patent fails to teach a particular reason to select the claimed subgenus. In fact, exendin-4 (or exenatide) was not a known therapeutic at the time of the '130 Patent. As such, it would not have been obvious for one of skill in the art to select the claimed species or subgenus from that disclosed in the '130 Patent.

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103 be withdrawn.

Claim 44 stands rejected under 35 U.S.C. §103(a) as being allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; "the '130 Patent") in view of Young et al. (US 2003/0087820), as applied to claims 1, 3-43, and 45-46 and further in view of Crotts et al. (US 2003/0017203). Applicants respectfully traverse the rejection as it applies to the pending claims.

For the reasons presented above, Applicants reassert that the claimed invention is not obvious in view of the '130 Patent. Additionally, the teachings of Ladner et al. fail to cure the deficiencies of the '040 patent. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 44.

Rejections Under Nonstatutory Obviousness-type Double Patenting

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 stand rejected under the judicially created doctrine of obviousness double patenting as allegedly obvious over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (hereafter "the '130 Patent") in view of Young et al. (US 2003/0087820). Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom.

For the reasons presented above, Applicants reassert that the claimed invention is not obvious in view of the '130 Patent. Additionally, the teachings of Young et al. fail to cure the deficiencies of the '040 patent. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 stand provisionally rejected under the judicially created doctrine of obviousness double patenting as allegedly obvious over claims 1-6 and 12-13 of copending U.S. Patent Application No. 11/193,825. Applicants respectfully request the provisional rejection be held in abeyance until allowable claims are determined in the present application.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of $635.00 as payment for the Request for Continued Examination fee ($405.00) and Two-Month Petition for Extension of Time fee ($230.00) for small entity. No other fees are deemed necessary with the filing of this paper. However if any additional fees are due, the Commissioner is further authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: August 25, 2008

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USPTO Customer No. 28213

PTO/SB/22 (12-04)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) AEGIS1210
Application Number 11/127,786	Filed May 11, 2005
For ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION	
Art Unit 1616	Examiner J.H. ALSTRUM ACEVEDO

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☒	Two months (37 CFR 1.17(a)(2))	$460	$230	$ 230.00
☐	Three months (37 CFR 1.17(a)(3))	$1050	$525	$
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 07-1896 referencing the attorney docket number identified above.

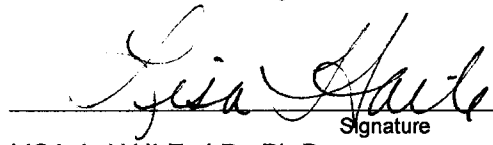
WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 38,347

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____.



Signature — August 25, 2008 (Date)

LISA A. HAILE, J.D., Ph.D. (Typed or printed name) — (858) 677-1456 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 form is submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	11127786
Filing Date:	11-May-2005
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Filer:	Lisa A. Haile/Karen LePari
Attorney Docket Number:	AEGIS1210

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	230	230

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	405	405
		Total in USD ($)		**635**

Electronic Acknowledgement Receipt

EFS ID:	3836735
Application Number:	11127786
International Application Number:	
Confirmation Number:	5393
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Customer Number:	28213
Filer:	Lisa A. Haile/Karen LePari
Filer Authorized By:	Lisa A. Haile
Attorney Docket Number:	AEGIS1210
Receipt Date:	25-AUG-2008
Filing Date:	11-MAY-2005
Time Stamp:	19:19:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$635
RAM confirmation Number	3970
Deposit Account	071896
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		AEGIS1210.pdf	809429 5e55c5c1fd7fb072ac31e7fd9bf51fc2d42e7ce5	yes	18

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Request for Continued Examination (RCE)	1	1
Amendment After Final	2	17
Extension of Time	18	18

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	31826 ffcb6470a3477e7faf109fc37c1bacc9f520fab2	no	2

Warnings:

Information:

Total Files Size (in bytes):	841255

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
11/127,786	05/11/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/25/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 28	Minus	** 46	= 0	X $25 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $105 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GOIGA N. DUCKETT/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,786	05/11/2005	Elias Meezan	AEGIS1210	5393

28213 7590 08/01/2008

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
08/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on *24 June 2008* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☒ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *Claims 3 and 32 have been amended, but are listed as being original claims. Appropriate correction is required.*.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

  _____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

_____ _____

Legal Instruments Examiner (LIE), if applicable Telephone No.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 11/127,786	**Applicant(s)** MEEZAN ET AL.	
	Examiner JAMES H. ALSTRUM ACEVEDO	**Art Unit** 1616	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 June 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1 and 3-46*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 6/10/08
13. ☒ Other: See Continuation Sheet.

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616

7/31/08

Continuation of 13. Other: Applicants' claims will not be entered for the reasons set forth herein. Claim 139 omits essential elements (i.e. the amount of surfactant necessary to increase the stability and bioavailability of exendin-4; see claims 140-141 for example). Claim 142 is a substantial duplicate of claim 141 because it recites the same method steps, active agent, surfactants, and amount of surfactants. Regarding the 112, 1st rejections concerning claim 24 and claims dependent therefrom, Applicants' Figure 1 only demonstrates the relative bioavailability of intranasal vs. intravenous administration for three compositions with or without added alkylglycoside. However, proposed amended claim 24 requires that the claimed composition is characterized by an area under curve (AUC) for the biologically active compound (i.e. exendin-4) in blood plasma that is 20% or greater than the AUC for the same biologically active compound following intramuscular injection. Data for relative intranasal/intravenous bioavailability (i.e. data in Applicants' Figures 1 through 3) is not considered to support the calculation/extrapolation of AUC for intramuscular administration or AUC in blood plasma. Regarding the rejections under 35 USC §103(a), Applicants amendments and arguments are found unpersuasive, because Applicants' attack the references individually and do not substantively address what the combined references allegedly lack to properly demonstrate obviousness. Furthermore, the Examiner emphasizes that it has clearly been demonstrated by the cited references that exendin-4 is art-recognized as having a similar physiological effect as glucagon and insulin. Thus, the combination or substitution of glucagon or insulin for exendin-4 is considered prima facie obvious as set forth on the record (see pages 15-20 of the final office action mailed on 3/24/08). Similarly. Applicants' arguments regarding the provisional and non-provisional obviousness-type double patenting rejections are also found unpersuasive and are maintained.

Receipt date: 06/24/2008

DO NOT ENTER: /J.H.A.A./ 7/30/08

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO THE FINAL OFFICE ACTION

Sir:

Responsive to the Final Office Action mailed March 24, 2008, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
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RESPONSE TO THE FINAL OFFICE ACTION

Sir:

Responsive to the Final Office Action mailed March 24, 2008, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Amendments to the Claims

Please amend claims 1, 3, 14-16, 18, 23-24, 28, 31-32 and 40-42 as provided below.

Please cancel claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35, 39, 45 and 46 without prejudice or disclaimer.

Please add new claims 139-142.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A surfactant composition comprising at least one alkyl glycoside or at least one saccharide alkyl ester admixed with a drug, wherein the surfactant maintains the biological activity and increases the bioavailability~~,~~ of the drug, wherein the drug is exendin-4 and the surfactant is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

2. (Canceled)

3. (Original) The composition of claim 1, wherein the ~~surfactant~~ composition has a ~~high~~ no observable adverse effect level (NOAEL) that is acceptable for daily intake.

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. (Original) The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. (Canceled)

9. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. (Original) The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. (Previously presented) The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system of a subject.

13. (Canceled)

14. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 20% (w/~~v~~).

15. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 5% (w/~~v~~).

16. (Currently amended) The composition of claim 1, wherein the surfactant is at a concentration of about 0.01% to 2% (w/~~v~~).

17. (Canceled)

18. (Currently amended) The composition of claim ~~17~~, wherein the composition has a pH less than 8.0.

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Currently amended) The ~~therapeutic~~ composition according to claim 1~~7~~, wherein the composition is formulated for mucosal administration to a subject.

24. (Currently amended) The ~~therapeutic~~ composition according to claim 1~~7~~, wherein administration to a subject yields enhanced mucosal delivery of said biologically active compound(s) ~~comprising:~~ characterized by

~~a) a peak concentration (C_{max}) of the biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of the subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;~~

~~b)~~ an area under concentration curve (AUC) of the biologically active compound(s) ~~in the central nervous system (CNS) tissue or fluid or~~ in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in ~~CNS or~~ blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject~~; or~~

~~c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours~~.

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Currently amended) The ~~therapeutic~~ composition of claim 1~~7~~, wherein the composition following mucosal administration to a subject yields an area under concentration curve (AUC) of the biologically active compound(s) ~~in the CNS tissue or fluid or~~ in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in the ~~CNS or~~ blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. (Canceled)

30. (Canceled)

31. (Currently amended) A method of administering a drug composition via ocular, nasal, intranasal or intraperitoneal routes comprising a surfactant that increases the bioavailability of the drug having at least one alkyl glycoside ~~or saccharide alkyl ester~~ mixed with at least one drug and delivered to a subject, wherein the drug is exendin-4 and the alkyl has from about 10 to 24 carbon atoms and is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside~~, and the surfactant increases the bioavailability of the drug wherein the drug is exendin-4~~.

32. (Original) The method of claim 31, wherein the ~~surfactant~~ composition has a ~~high~~ no observable adverse effect level (NOAEL) that is acceptable for daily intake.

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Previously presented) The method of claim 31, wherein the surfactant reduces variance in bioavailability from patient to patient.

37. (Previously presented) The method of claim 31, wherein the composition does not enter the hepatic portal blood system of a subject.

38. (Previously presented) The method of claim 31, wherein the composition has a pH less than 8.0.

39. (Canceled)

40. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 20% (w/~~v~~).

41. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 5% (w/~~v~~).

42. (Currently amended) The method of claim 31, wherein the surfactant has a concentration of about 0.01% to 2% (w/~~v~~).

43. (Original) The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. (Previously presented) The composition of claim 1, wherein the composition further comprises an enteric coating.

45. (Canceled)

46. (Canceled)

47. – 138. (Canceled)

139. (New) A method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

140. (New) The method of claim 139, wherein the surfactant is at a concentration of about 0.25% (w).

141. (New) The method of claim 139, wherein the surfactant is at a concentration of about 0.5% (w).

142. (New) A method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is at a concentration of about 0.5% (w) and is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside .

REMARKS

In the present amendment, claims 1, 3, 14-16, 18, 23-24, 28, 31-32 and 40-42 have been amended; claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35, 39, 45 and 46 have been canceled without prejudice or disclaimer; and new claims 139-142 have been added. The amendments add no new matter as the claim language is fully supported by the specification and original claims.

Rejections under 35 U.S.C. §112, First Paragraph (written description)

Claims 17-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

It is well-established that an objective standard for determining compliance with the written description requirement is, whether the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see, *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed (see, *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and MPEP §2163.04).

The Office Action alleges the specification does not describe any compositions characterized by stability of the biologically active compound for at least 6 months at temperatures from about 4°C to 25°C in sufficient detail to demonstrate possession at the time the instant application was filed. Additionally, the Office Action further alleges that the specification lacks data or written support to demonstrate that Applicants were in possession of compositions characterized by peak concentration values (C_{max}), area under the curve (AUC) and time to maximal concentration (t_{max}) as recited in claims 23-30 because there allegedly is no such data presented in the specification or figures.

Without acquiescing to the reasoning presented in the Office Action, and in order to expedite prosecution of the instant application, Applicants have canceled claims 17, 19-22, 25-27, 29-30, 33-35 and 39, without prejudice or disclaimer rendering the rejection moot as to such claims. Additionally, claims 18, 23, 24 and 28 have been amended to depend from claim 1 which does not recite the rejected stability characteristics (*e.g.*, "maintains the biological activity of the drug, for at least about 6 months from about 4°C to 25°C") rendering the rejection moot as to such claims. Further, claims 45 and 46 depend from claim 1 rendering the rejection moot as to such claims. With regard to amended claims 24 and 28, the claims have been amended by deleting reference to C_{max}, t_{max} and "CNS tissue" to clarify that the AUC is of blood plasma. Determination of bioavailability is discussed in the specification as filed, for example, in paragraphs [0074] and [0075] and Applicants respectfully submit that AUC may be readily extrapolated from Figure 1 which is discussed in Example 2 because bioavailability is directly derived from a simple comparison of proportions of AUC for an intravenous and oral dosage.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 14-16, 20-22 and 40-42 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office Action alleges that the specification does not support concentrations of surfactant in units of weight/volume (w/v), but rather supports concentrations expressed as weight percentages as shown in paragraphs 70 and 88. Without acquiescing to the reasoning presented in the Office Action, and in order to expedite prosecution of the instant application, Applicants have canceled claims 20-22 without prejudice or disclaimer rendering the rejection moot as to such claims. Additionally, Applicants have amended claims 14-16 and 40-42 to reflect concentrations in weight percentages as suggested in the Office Action.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph (enablement)

Claims 31-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims. Claims 33-35 and 39 have been canceled without prejudice or disclaimer rendering the rejection moot as to such claims.

The Office Action alleges that while exendin-4 is enabled, it is allegedly only enabled for methods of administering exendin-4 in combination with an alkyl glycoside selected from the group consisting of dodecyl sucrose (DDS), dodecyl maltoside (DDM), tridecyl maltoside (TDM) and tridecyl maltoside (TriDM) via ocular, nasal, intranasal, or intraperitoneal administration (see the Office Action, page 10 last paragraph through page 11, first and second paragraphs).

Without acquiescing to the reasoning presented in the Office Action and in order to expedite prosecution of the present application, Applicants have amended claim 31 to recite as follows:

> 31. A method of administering a drug composition via ocular, nasal, intranasal or intraperitoneal routes comprising a surfactant that increases the bioavailability of the drug having at least one alkyl glycoside mixed with at least one drug and delivered to a subject, wherein the drug is exendin-4 and the alkyl has from about 10 to 24 carbon atoms and is selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claims 3-6 and 32-35 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

Specifically, the Office Action also alleges that claims 3-6 and 32-35 contain the indefinite term "high". Without acquiescing to the reasoning presented in the Office Action and in order to expedite prosecution of the instant application, Applicants have canceled claims 4-6 and 33-35 without prejudice or disclaimer. Additionally, Applicants have amended claims 3 and 32 to recite that the "composition has a no observable adverse effect level (NOAEL) that is acceptable for daily intake". As such, the claim no longer recites the term "high".

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1, 3-43 and 45-46 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter "the '130 Patent") in view of Young et al. (US 2003/0087820). Applicants respectfully traverse the rejection as it applies to the pending claims. Claims 4-6, 8, 13, 17, 19-22, 25-27, 29-30, 33-35 and 39 have been canceled rendering the rejection moot as to such claims.

The recent U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the

general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness with regard to the amended claims, because there would be no motivation for one of skill in the art to combine the references. The Office Action concedes that the '130 Patent fails to specifically teach compositions including exendin-4. To cure the deficiency, the Office Action utilizes Young et al. and alleges that Young et al. teaches compositions comprising exendin-4 for any known route of administration, such as intranasal administration. Applicants respectfully disagree and point out that Young et al. fails to teach administration via the ocular route as presently recited in claim 31. Additionally, the compositions disclosed in Young et al. are formulated for extended release and utilize an ionic surfactant, such as alkali polyether alcohol sulfates or sulfonates (*e.g.* Triton) or a surfactant of polysorbate 80 or other non-ionic detergent such as Tween. Applicants respectfully submit that there would be no motivation for one of skill in the art to combine the references to practice the inventions presently claimed which includes the proviso that the surfactant maintains the biological activity and increases the bioavailability of the drug. Applicants respectfully submit that neither reference discloses maintaining the biological activity and increasing the bioavailability of the exendin-4 and therefore one of skill in the art would not have been motivated to utilize exendin-4 in combination with the claimed surfactants to achieve the claimed characteristics.

Even if one were to modify the '130 Patent, there is no *prima facie* case of obviousness as to the amended claims, because there would be no expectation of successfully practicing the claimed invention. None of the cited references provide sufficient guidance to ensure a reasonable expectation of success of practicing the claimed invention given the unpredictability in the art.

The cited references fail to disclose any formulations including exendin-4 in combination with an alkylglycoside surfactant, especially any of the surfactants claimed. Additionally, the cited references fail to disclose any guidelines as to amounts of peptide or protein that may be

used or amounts of alkylglycoside to be utilized with exendin-4. Without such teachings, Applicants respectfully submit that there could have been no reasonable expectation of success in carrying out the claimed invention because the prior art fails to sufficiently teach how one of skill in the art would go about practicing the claimed invention.

With regard to new claims 139-142, Applicants respectfully submit that the subject matter of such claims is not obvious over the '130 Patent. As recited, new claim 139 is directed to a "method of administering a drug composition via nasal, nasalocrimal, inhalation or pulmonary routes comprising mixing exendin-4 with a sufficient amount of a surfactant to increase the stability and bioavailability of exendin-4 and delivering the composition to a subject, wherein the surfactant is an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, tridecyl maltoside and tetradecyl maltoside." Additionally, claims 140 and 141 recite specific concentrations of alkyl glycoside to be utilized, while new claim 142 is directed to intranasal administration of exendin-4 in combination with dodecyl sucrose, dodecyl maltoside or tridecyl maltoside at a concentration of 0.5%.

Applicants respectfully submit that the '130 Patent fails to disclose intranasal administration of exendin-4 in combination with dodecyl sucrose, dodecyl maltoside, tridecyl maltoside or tetradecyl maltoside at the recited concentrations, 0.5% (w) or 0.25% (w). While the '130 Patent discloses broad concentration ranges of alkyl glycosides and includes examples utilizing ocular administration of insulin, the '130 Patent fails to teach intranasal administration alone using the specific alkyl glycosides and concentrations recited in the new claims as well as increasing the stability and bioavailability of the drug at such concentrations. Applicants submit that without such teachings, the claimed invention would not have been obvious to one of skill in the art because there could be no reasonable expectation of successfully practicing the claimed invention. Given the unpredictability inherent in drug formulation combined with the variations of absorption across different types of epithelial cells, as well as the individual characteristics of exendin-4 and specific alkyl glycosides at specific concentrations, the formulation for intranasal administration including exendin-4 in combination with specific alkyl glycosides at specific

concentrations sufficient to increase stability and bioavailability of exendin-4 would not have been obvious to one of skill in the art.

Additionally, Applicants respectfully submit that the present claims encompass a defined subgenus of that disclosed and claimed in the '130 Patent. The fact that a claimed species or subgenus is encompassed by a prior art genus does not establish a *prima facie* case of obviousness (see, *In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). Applicants respectfully submit that the genus disclosed in the '130 Patent is broad and encompasses vast combinations of alkyl glycosides, concentrations, and drugs. Additionally, the '130 Patent fails to teach a particular reason to select the claimed subgenus. In fact, exendin-4 (or exenatide) was not a known therapeutic at the time of the '130 Patent. As such, it would not have been obvious for one of skill in the art to select the claimed species or subgenus from that disclosed in the '130 Patent.

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103 be withdrawn.

Claim 44 stands rejected under 35 U.S.C. §103(a) as being allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; "the '130 Patent") in view of Young et al. (US 2003/0087820), as applied to claims 1, 3-43, and 45-46 and further in view of Crotts et al. (US 2003/0017203). Applicants respectfully traverse the rejection as it applies to the pending claims.

For the reasons presented above, Applicants reassert that the claimed invention is not obvious in view of the '130 Patent. Additionally, the teachings of Ladner et al. fail to cure the deficiencies of the '040 patent. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 44.

Rejections Under Nonstatutory Obviousness-type Double Patenting

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 stand rejected under the judicially created doctrine of obviousness double patenting as allegedly obvious over claims 1-5 and 8-10

of U.S. Patent No. 5,661,130 (hereafter "the '130 Patent") in view of Young et al. (US 2003/0087820). Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom.

For the reasons presented above, Applicants reassert that the claimed invention is not obvious in view of the '130 Patent. Additionally, the teachings of Young et al. fail to cure the deficiencies of the '040 patent. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 stand provisionally rejected under the judicially created doctrine of obviousness double patenting as allegedly obvious over claims 1-6 and 12-13 of copending U.S. Patent Application No. 11/193,825. Applicants respectfully request the provisional rejection be held in abeyance until allowable claims are determined in the present application.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: June 24, 2008

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA Piper US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO Customer No. 28213

Electronic Acknowledgement Receipt

EFS ID:	3512464
Application Number:	11127786
International Application Number:	
Confirmation Number:	5393
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Customer Number:	28213
Filer:	Lisa A. Haile/Karen LePari
Filer Authorized By:	Lisa A. Haile
Attorney Docket Number:	AEGIS1210
Receipt Date:	24-JUN-2008
Filing Date:	11-MAY-2005
Time Stamp:	19:40:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment After Final	AEGIS1210.pdf	674935 a045ab91e8c193d9df54ec1dd8d87f068b542b56	no	16

Warnings:	
Information:	

Total Files Size (in bytes):	674935

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/127,786	05/11/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/24/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 46	= 0	X $25 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 5	Minus	***3	= 2	X $105 =	210	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	210	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/EAON SMALLWOOD/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filing Date:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

After receipt of the Final Office Action and upon review of this case, it was discovered that the document set forth on the enclosed Form PTO-1449 was not cited in the present application. It is understood that the Office is under no obligation to consider this document at this time; however, to complete the record it is submitted.

While applicant believes that the document is in no way destructive of patentability of the allowed claims, in the interest of completeness, it is submitted herewith.

The Commissioner is hereby authorized to charge the amount of $180.00 as payment for the Information Disclosure Statement fee to Deposit Account No.: 07-1896. No other fee is deemed necessary with the filing of this paper. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 07-1896, referencing the above-identified attorney docket number.

Respectfully submitted,

Date: June 10, 2008

Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No.: 28213

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No.: AEGIS1210	Serial No.: 11/127,786
	Applicant(s): Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1616

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA	6,794,357	09/21/04	Backstrom et al.	514	2	10/24/96

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

EXAMINER	DATE CONSIDERED
WEST\21440450.1 356894-000012	

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449

Electronic Patent Application Fee Transmittal

Application Number:	11127786
Filing Date:	11-May-2005
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Filer:	Lisa A. Haile/Mikhail Puchkov
Attorney Docket Number:	AEGIS1210
Filed as Small Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	3435143
Application Number:	11127786
International Application Number:	
Confirmation Number:	5393
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Customer Number:	28213
Filer:	Lisa A. Haile/Mikhail Puchkov
Filer Authorized By:	Lisa A. Haile
Attorney Docket Number:	AEGIS1210
Receipt Date:	10-JUN-2008
Filing Date:	11-MAY-2005
Time Stamp:	21:45:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4422
Deposit Account	071896
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	AEGIS1210_IDS_XMTL_.pdf	43310 c986531f97d8fc82dfac96f117a5da0c74d41e65	no	2
Warnings:					
Information:					
2		AEGIS1210_IDS_.pdf	80959 9ae89b3a153793e39addf0b1dcac46ab14e087d3	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Information Disclosure Statement Letter	1	2
Information Disclosure Statement (IDS) Filed	3	3

Warnings:					
Information:					
3	Fee Worksheet (PTO-06)	fee-info.pdf	8166 b5c11d65aebc72fca863c494f79c9d94a7b9902e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	132435		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filing Date:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir:

Transmitted herewith for the above-identified application please find:

1. Information Disclosure Statement (2 pgs.); and
2. Form PTO-1449 (1 pg.)

The Commissioner is hereby authorized to charge the amount of $180.00 as payment for the Information Disclosure Statement fee to Deposit Account No.: 07-1896. No other fee is deemed necessary with the filing of this paper. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 07-1896, referencing the above-identified attorney docket number.

Respectfully submitted,

Date: June 10, 2008

Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
Customer Number: 28213

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/127,786	05/11/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 06/10/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 28	Minus	** 46	= 0	X $25 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $105 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/EAON SMALLWOOD/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,786	05/11/2005	Elias Meezan	AEGIS1210	5393

28213 7590 03/24/2008

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
03/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/14/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

U.S. Patent and Trademark Office

DETAILED ACTION

Claims 1 and 3-46 are pending. Applicants have newly cancelled claim 2. Claims 47-138 were previously cancelled. Applicants have amended claims 1, 4-6, 12, 14-18, 20-31, 33-38, 40-42, and 44-46. Receipt and consideration of Applicants' amended claim set, affidavits submitted under 37 CFR 1.132 (9/27/07 and 8/13/07), IDS (submitted 8/13/07), terminal disclaimer (submitted 8/13/07), replacement drawings (submitted 8/13/07), and arguments/remarks submitted on December 14, 2007 are acknowledged. Applicants' claim amendments have necessitated new grounds of rejection (e.g. a new rejection under 35 USC 112, 1st). Any rejections or objections of record that have not been explicitly maintained herein are withdrawn per Applicants' claim amendments.

Terminal Disclaimer(s)

The terminal disclaimer filed on 8/13/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,661,130 (USPN '130) was reviewed and accepted. The terminal disclaimer was recorded. In Applicants' most recent arguments filed on December 14, 2007, Applicants requested withdrawal of the terminal disclaimer filed on 8/13/07. Thus, the **terminal disclaimer filed on 8/13/07** disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,661,130 (USPN '130) **is withdrawn**.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/13/07 was filed after the mailing date of the office action on 2/12/07. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 17-46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained** for the reasons of record, which have been restated below for Applicants' convenience**.** The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' specification does not describe any of the following therapeutic compositions characterized by the stability of the biologically active compound being stabilized

for at least 6 months from about 4 °C-25 °C in sufficient detail to demonstrate possession at the time the instant application was filed: (1) a composition comprising (a) at least one biologically active compound, (b) at least one alkyl glycoside, and (c) at least one saccharide ester; (2) (a) at least one biologically active compound and (b) at least one saccharide ester; nor (3) (a) at least one biologically active compound and (b) at least one alkyl glycoside. The specification is bereft of any data for therapeutic compositions (1)-(3) demonstrating that these had the claimed stability. It is noted that the definitions of alkyl glycoside and alkyl saccharide ester are extremely broad and include glycosides and saccharide esters that are oligomeric and polymeric.

Applicants' specification lacks data or written support to demonstrate that Applicants' were in possession of stable therapeutic compositions (1)-(3) wherein administration of said compositions to any subject is characterized by (a) peak concentration values (C_{max}) in CNS tissue/fluid or blood plasma of any biological active compound in any subject is about 15% or more greater than the C_{max} in CNS tissue/fluid or blood plasma compared to intramuscular injection; (b) an area under curve (AUC) of the biologically active compound(s) in the CNS tissue/fluid or blood plasma of said subject that is 20% or greater compared to the AUC in the same subject's CNS tissue/fluid or blood plasma after intramuscular administration; and (c) a time to maximal concentration (t_{max}) of the biologically active agent in a CNS tissue/fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours. There is no AUC, t_{max}, or C_{max} data present in the instant specification or figures.

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that (1) the stability property generally claimed in claims 13, 19, and 39 is allegedly supported by U.S. Patent No. 5,726,154 (USPN '154), which is incorporated by reference into Applicants' specification, and teaches that "similar compositions" comprising sodium dodecyl sulfate (SDS) surfactant and an effective amount of an organic acid exhibit calcitonin stability for up to 6 months at between 4-25 °C; and (2) the bioavailability data presented, for example, in Figure 1 and paragraphs [0117]-[[0118] allegedly provide adequate information for an ordinary skilled artisan to extrapolate AUC, t_{max}, or C_{max} data in both blood plasma and CNS tissue/fluid.

The Examiner respectfully disagrees with Applicants' traversal arguments. The compositions described in USPN '154 are not similar to Applicants' claimed compositions, because the active agent in Applicants' claims, exendin-4, is a different unrelated protein than that exemplified in USPN '154 and the stabilizing surfactant used in USPN '154 is extremely structurally different than the surfactants being claimed in Applicants' compositions that allegedly convey the greater stability and enhanced absorption properties. It seems Applicants are implying that all surfactants, regardless of structure, convey increased stability to at least all aqueous protein compositions. Absent evidence substantiating Applicants' implied assertion of the general ability of all surfactants to stabilize all aqueous protein compositions, this is unpersuasive.

Regarding (2), Applicants arguments are unpersuasive, because the data provided in the specification is limited to blood plasma data. As Applicants are well aware, "bioavailability" is a

measure of the fraction dose of a drug that reaches systemic circulation (i.e. systemic circulation = blood plasma levels)[1]. Bioavailability is not a measure of drug levels found in the CNS tissue/fluid. Furthermore, as was clearly set forth in the enablement rejection of the previous office action, passage of drugs across the blood-brain barrier and into the CNS fluid/tissue is very difficult and Applicants have not demonstrated nor does the prior art recognize that alkyl glycosides and saccharide esters as generally exhibiting the property of enhancing absorption of drugs into the CNS fluid/tissue. Applicants have provided no data corroborating the claimed CNS tissue/fluid AUC, t_{max}, or C_{max} values. Regarding AUC, t_{max}, or C_{max} in blood plasma, to calculate these data an ordinary skilled artisan would require knowledge of drug dosage and would have to unreasonably assume that (1) administration of the drug dosage was 100% efficient; (2) no drug was cleared upon administration, such as by 1st pass metabolism in the liver; and (3) the administered drug was homogenously distributed throughout all organs, tissues, etc. Thus, an ordinary skilled artisan could not extrapolate the AUC, t_{max}, or C_{max} data recited in Applicants claims based upon the bioavailability data in Applicants' specification as set forth above.

Claims 14-16, 20-22, and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' specification does

[1] See Birkett et al. 1991, Vol. 14, pp 14-16, which was submitted on Applicants' new IDS, filed on 8/13/07.

not support concentrations of surfactant expressed in units of w/v. Rather, Applicants specification only supports surfactant concentrations as expressed as weight percentages (see, for example, paragraphs 70 and 88).

The rejection of claims 31-46 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering a drug composition comprising insulin, glucagon, or exendin-4 in combination with an alkyl glycoside selected from the group consisting of tetradecyl maltoside, dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside via ocular, nasal, intranasal, or intraperitoneal administration, does not reasonably provide enablement for the administration of compositions comprising exendin-4 in combination with any other alkyl glycoside or any alkyl saccharide ester **is maintained** for the reasons of record, which have been restated in amended form below for Applicant's convenience and to address Applicants claim amendments limiting the active agent to exendin-4**.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co*., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re*

Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad. Applicants' are claiming a method of administering via any route of administration to any subject a composition comprising any drug, any alkyl glycoside, and/or any saccharide alkyl ester, wherein alky has from about 10-24 carbon atoms. The term subject is not defined in the specification. A reasonable broad interpretation of the word "subject" includes any living organism to which biologically active agents could be administered, such as amoeba, bacteria, fungi, trees, grasses, shrubs, humans, mammals, reptiles, fish, birds, invertebrates, and vertebrates. The term drug is defined in [0055] to include any molecule or therapeutic agent or therapeutic compound or biologically active compound. The term biologically active is not defined, therefore any molecule or compound that could have an effect on a biological system is biologically active, such as cyanide, elemental iron, elemental mercury, methyl mercury, DNA, RNA, antibiotics, proteins, enzymes, any organic molecule (e.g. salicylic acid, phosgene, chloromethyl methyl ether, etc.) water, etc. The terms alkyl glycoside and saccharide alkyl ester are extremely broad, with only the limitation on the length of the alkyl groups somewhat limiting the scope. It is noted that there is no limitation on the number of alkyl groups a given alky glycoside or saccharide alkyl ester could have.

Nature of the invention/State of the Prior Art

The invention claims methods of administering to a subject a drug composition comprising a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alky has from about 10-24 carbon atoms and the surfactant increases the stability and bioavailability of the drug.

Routes of administration are known in the art, such as oral, buccal, nasal, rectal, vaginal, ocular, urethral, intrathecal, inhalation, injection (intramuscular, intravenous, intraperitoneal), etc. These various routes of administration often require that administered compositions have specific requirements. For example, inhalation administration requires that the inhaled compositions are characterized as aerosols (particulate solids or liquids suspended in an air or gas stream) having particle sizes below 10 microns (see Fig. 1 in Radhakrishnan et al. (U.S. Patent No. 5,192,528)) as well as other desirable aerodynamic properties (e.g. a density below 0.4 g/cm^3; See Edwards, USPN 6,254,854; e.g. col. 2, lines 1-60). Compositions intended for nasal or parenteral administration should be isotonic with the tissues through which or into which administration occurs and have a compatible pH (e.g. a pH between 4-7; see, for example, US 2003/0158206; or USPN 6,482,834; e.g. col. 36, line 1 through col. 37, line 6). The prior art also recognizes that administration of drugs resulting in the absorption of drugs into CNS tissue/fluids is difficult (Beam et al. "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antibiotics in Rabbits with Intact and Inflamed Meninges," *Antimicrobial Agents and Chemotherapy*, **1977 (Dec.)**, *12(6)*, pp 710-716). ***Not all drugs are capable of crossing the blood brain barrier in detectable concentrations that would indicate absorption/bioavailability of these drugs in CNS tissue/fluids*** (pg. 712, right column, 2nd paragraph). Furthermore, a subjects' overall health

could affect the ability of drugs to be absorbed by CNS tissues/fluids. For example, it was observed that in rabbits afflicted with pneumoccocal meningitis that tobramycin, an antibiotic, was measurable in cerebrospinal fluid (CSF), but not in brain tissue (abstract; pg. 710).

The prior art recognizes that ***some*** alkyl glycosides are characterized by the ability to enhance penetration (i.e. absorption) of drugs across mucosal epithelia and thereby the bioavailability of said drugs (e.g. Kee et al. USPN 5,369,095; IDS reference, Example 10, col. 11, lines 13-31 and Example 8, col. 10, lines 28-64). The alkyl glycosides that have this capability have alkyl groups ranging in length from 8 to about 14 carbon atoms and are comprised of monosaccharides (e.g. glucose or inositol) and disaccharides (i.e. maltose and sucrose). ***The prior art does not teach that polymeric or oligomeric alkyl glycosides (e.g. alkyl glycosides wherein the saccharide component is starch, cellulose, or chitin, for example) exhibit this same property. The prior art does not teach that saccharide alkyl esters have the property of enhancing absorption/penetration of drugs across mucosal epithelia.***

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants' provide data demonstrating the ability of formulations comprising one alkyl glycoside selected from tetradecylmaltoside (TDM), dodecyl sucrose (DDS), dodecyl maltoside

(DDM), and tridecyl maltoside (TriDM) promote absorption of drugs when administered intranasally (TDM only), ocularly (i.e. as eye drops), or interperitoneally (TDM only) to enhance the absorption of drugs (i.e. insulin, glucagon, and exenedin-4) and as a result increase the bioavailabilty of said drugs. ***Applicants' have not provided any data demonstrating that compositions comprising a saccharide alkyl ester and exendin-4 also exhibit similar increases in absorption and bioavailability.*** In fact, there is **not a single example of any composition comprising any saccharide ester in Applicants' specification, which demonstrates the ability of a saccharide alkyl ester to enhance the absorption and stability of exendin-4**. Applicants' data is only limited to blood plasma data. Applicants' data is not related to AUC, t_{max}, or C_{max}. Applicants' have not provided evidence that the property of increased absorption/bioavailability attributed to the presence of any of the alky glycosides discussed above (i.e. TDM, DDS, DDM, and TriDM) can be extrapolated to absorption and bioavailability in CNS fluids/tissue.

In summary, the Examiner concludes that Applicants are only enabled for methods of administering a drug composition comprising insulin, glucagon, or exendin-4 in combination with an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside via ocular, nasal, intranasal, or intraperitoneal administration. Applicants' have not provided sufficient data and description to enable a person of ordinary skill in the art to administer compositions comprising any other biologically active agent in combination with any other alkyl glycoside (e.g. polymeric or oligomeric alkyl glycosides) or any alkyl saccharide ester. This lack of enablement would force the ordinary skilled artisan to undertake burdensome experimentation to discover (1) which other alkyl glycosides (e.g.

oligomeric and polymeric alkyl glycosides) to use; (2) which saccharide alkyl esters, if any, are suitable; and (3) how to formulate these compositions to enable absorption/bioavailability in CNS tissue/fluid as well as administer said compositions via other routes (e.g. orally or by inhalation).

To emphasize this point the Examiner directs Applicants to "Genentech, 108 F.3d at 1366 and *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)" which states,

> "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that (1) the rejection is improper because the claims now recite that the active agent is exendin-4; (2) the term "biologically active agent" is understood by ordinary skilled artisans; and (3) that an ordinary skilled artisan would understand what constitutes a subject by the description in paragraph 10 of Applicants' specification to mean any organism with oral, ocular, nasal, etc. routs of administration.

The Examiner respectfully disagrees. Regarding (3) the paragraph cited in Applicants' arguments is not paragraph 10 as found in Applicants' specification. Rather, paragraph 10 as present in Applicants' specification reads,

"[0010] The present invention also provides a method of treating congestive heart failure in a subject including administering to the subject in need thereof via the oral, ocular, nasal, nasolacrimal, or inhalation delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing

amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject."

Nonetheless, although an ordinary skilled artisan upon reading the alleged paragraph 10 would read the term "subject" to mean organisms to which oral, ocular, nasal, etc. routes of administration or possible, this term remains broad. Similarly, regarding (2) the term "biologically active" remains broad and is not defined in Applicants' specification in limiting manner. Concerning (1), Applicants specification does not identify a single saccharide ester that enhances absorption of exendin-4, or any other drug, via any route of administration. Furthermore, concerning the broad genus of alkyl glycosides, the demonstration that 4 structurally similar species exhibit the properties of enhancing absorption does not enable an ordinary skilled artisan to make the claimed compositions exhibiting the same properties from any of the other species contained within a genus comprising potentially several thousands or even millions of compounds.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3-6 and 32-35 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record restated herein below.

The term "high" in claims 3-6 and 32-35 is a relative term, which renders the claim indefinite. The term "high no observable adverse effect level" (i.e. high "NOAEL") is not defined by the claim, the specification does not provide a standard for ascertaining the requisite

degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted that the cited claims state that the claim states that the "NOEL" is a certain factor higher than the daily intake amount of the surfactant; however, the claim does not state what the daily intake amount for any surfactant is. Therefore, an ordinary skilled artisan would not be apprised of the metes and bounds of what constitutes a high NOEAL.

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that paragraphs [0049]-[0051] of Applicants' specification describe the term "high" with sufficient clarity to convey to the skilled artisan the meaning of the term high NOAEL.

The Examiner respectfully disagrees with Applicants' traversal argument; because said paragraphs do not define high NOAEL and examples do not constitute definitions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-43, and 45-46 under 35 U.S.C. 103(a) as being unpatentable over Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130") in view of Young et al. (US 2003/0087820).

Applicant Claims

Applicants claim (1) a surfactant composition comprising at least one alkyl glycoside and/or at least one saccharide alkyl ester; (2) a therapeutic composition comprising at least biologically active compound(s) and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or saccharide alkyl ester, wherein said composition stabilizes

the biological activity of the drug for at least 6 months from about 4°C to about 25°C; and (3) a method of administering a drug composition, wherein the drug composition a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10-24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meezan '130 were set forth in the previous office action, and are restated herein. Meezan discloses in claims 1-5 and 8-10:

1. A method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

2. The method of claim **1**, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

3. The method of claim **1**, wherein the alkyl has from 9 to 24 carbons.

4. The method of claim **3**, wherein the alkyl has from 9 to 14 carbon atoms.

5. The method of claim **4**, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

8. The method of claim **1**, wherein the compound is a protein or a peptide.

9. The method of claim **8**, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

10. The method of claim **8**, and further comprising administering a protease or peptidase inhibitor.

Meezan discloses that preferred **glycosides include maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12, or 14 carbon atoms** (col. 6, lines 46-51). Compounds which can exhibit an increased absorption by Meezan's invented method include **peptide hormones (e.g. insulin, calcitonin, enkephalins, glucagon), hypoglycemic agents (e.g. tolbutamide and glyburide**), and agents which are poorly absorbed by enteric routes (e.g. friseofulvin) (col. 5, lines 17-32).

The claimed properties of the claimed surfactants are inherent to these compounds. Wherein the prior art discloses the same compounds, these must have the same properties, because a compound and its properties may not be separated.

Young teaches exendin and exendin agonist formulations suitable for any known route of administration, such as intranasal administration. Exendin-4 is a known naturally occurring hormonal peptide that is known to have a longer duration of effect than GLP-1, and similar to GLP-1 has been demonstrated to lower glucose levels in diabetic mice (title; abstract; Figure 10; [0047]; [0224]-[0227]; [0231]-[0239]; Examples 1-7 and Example 9).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meezan '130 lacks the teaching of a composition comprising exendin-4. This deficiency is cured by the teachings of Young.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Meezan '130 and Young, because Meezan teaches that the invented compositions comprising absorption enhancers may comprise peptidic hormones as the active agent (i.e. insulin or glucagon) and Young teaches compositions comprising a peptidic hormone (e.g. exendins, such as exendin-4). It would have been prima facie obvious to modify Meezan's compositions to utilize exendin-4 in addition to insulin or in lieu of insulin, because exendin is known to be suitable for lowering blood glucose in diabetic

mice, which is an analogous function accomplished by the administration of insulin. The functional similarity in the therapeutic effect of insulin and exendin-4 with regards to the lowering of blood glucose would provide the ordinary skilled artisan with motivation to modify Meezan's compositions and would also have provided a reasonable expectation of success upon addition of exendin-4 to or in place of insulin in Meezan's compositions. Regarding the stabilizing, high NOAEL, and antibacterial properties recited in Applicants' compositions, these properties are attributed to alkyl glycoside surfactants, including the very same alkyl glycoside surfactants utilized in Meezan's formulations. Thus, Meezan's formulations necessarily would exhibit the same properties, because a compound and its properties are inseparable regardless of whether the prior art recognized the presence of said properties. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130") in view of Young et al. (US 2003/0087820), as applied above to claims 1, 3-43, and 45-46, and further in view of Crotts (US 2003/0017203; already of record).

Applicant Claims

Applicants claim a composition as described above which further comprises an enteric coating.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meezan and Young have been set forth above in the instant office action. Crotts teaches an oral peptide pharmaceutical dosage form for the oral delivery of a peptide composition that includes an absorption enhancer effective to promote the bioavailability of the peptide and an **enteric coating** (title; abstract; claims 1 and 16-17). Crotts teaches that the invention is suitable for patients who suffer from disorders or diseases that are treatable by administration of a peptide [0013]. Suitable enteric coatings are described in [0034]-[0036]. Crotts focuses on the administration of calcitonin ([0013]; claims).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meezan '130 lacks the teaching of a composition further comprising an enteric coating. This deficiency is cured by the teachings of Crotts.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Meezan/Young and Crotts, because Meezan/Young teach compositions comprising absorption enhancers and the same active agent (i.e. calcitonin) taught as being the active peptide in Crotts compositions. An ordinary skilled artisan would have been motivated to combine the teachings of Meezan/Young and Crotts because Crotts teaches that the invented compositions comprise absorption enhancers and can comprise any peptide that is useful in the treatment of a disease or condition, such as calcitonin, and Meezan/Young

teaches calcitonin compositions comprising alkyl glycoside absorption enhancers. An ordinary skilled artisan would have been further motivated to combine the teachings of Meezan and Crotts, because the presence of an enteric coating in Crotts compositions when combined with the teachings of Meezan/Young would enable the oral administration of calcitonin, exendin-4, and other active peptide formulations. Because the enteric coating of Crotts compositions would be expected to prevent the degradation of peptide active agents, such as calcitonin, exendin-4, or insulin, an ordinary skilled artisan would have had a reasonable expectation of success upon modification of the teachings of Meezan with the teachings of Crotts.

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that Crotts allegedly teaches away from the recited composition stability based on teachings that "15% of the drug could not be accounted for from 0.5 mg tablet after six months of storage at ambient temperature." This is found unpersuasive, because the claim 44 does not recite any particular required composition stability. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., composition stability for at least six months from about 4-25 °C) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 14-17, 20-23, 31, 40-42, 43, and 45-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (USPN '130) in view of Young et al. (US 2003/0087820). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. It is noted that the cited claims of USPN '130 are drawn to methods of increasing absorption of a compound into the circulatory system comprising administration of a compound and an absorption increasing amount of a suitable non-toxic, nonionic alkyl glycoside. It is noted that dependent claims 8-10 of USPN '130 specify that the compound in the composition is a protein or peptide, such as insulin and glucagon, and/or method further comprises the administration of a protease or peptidase inhibitor. The main

difference between the claims of the instant application and the claims of USPN '130 do not recite that the compositions comprise exendin-4. Nonetheless, the claims of USPN "130 indicate that the claimed compositions may comprise peptidic hormones, such as insulin and glucagon. The teachings of Young cure this deficiency and have been set forth above. Young clearly teaches that exendin-4 has been shown to reduce blood glucose levels in diabetic mice as well as healthy human volunteers. Lowering blood glucose levels is also a well known effect of insulin. Thus, it would have been prima facie obvious to an ordinary skilled artisan to add exendin-4 to the compositions utilized in Meezan's claimed method. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). The compositions utilized in the claimed methods of USPN '130 obviate the cited composition claims of the instant application. Regarding the claimed properties indicated as being due to the presence of alkyl glycoside surfactants in Applicants' claims, these properties would necessarily be present in the compositions utilized in the claimed methods of USPN '130, because these compositions comprise the same alkyl glycoside surfactants indicated by Applicants as providing the stabilization, anti-microbial, and high NOAEL properties. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that claims of the instant application are *prima facie* obvious over claims 1-10 of USPN '130.

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing (1) that the Examiner has failed to set forth a prima facie case of obviousness per Applicants' claim amendments and (2) an obviousness-type double patenting rejection over the cited claims of USPN '130 is allegedly improper, because USPN '130 is not commonly owned with the instant application.

The Examiner respectfully disagrees. Regarding (1), this has been addressed by the teachings of Young, which have been set forth above in the instant office action. Regarding (2), a proper non-statutory obviousness-type rejection requires (1) one or more common inventors ***and/OR*** (2) commonly owned/assigned or non-commonly assigned/owned but subject to a joint research agreement. See MPEP §804, Chart IIB. The instant application has one common inventor with USPN '130 (i.e. Meezan). Furthermore, Applicants' arguments/remarks have set forth that the instant application is owned and assigned to both The UAB Research Foundation (i.e. based upon Dr. Elias Meezan's and Dr. Dennis Pillion's assignment) and Aegis Therapeutics (i.e. based upon Dr. Edward Maggio's assignment). The UAB Research Foundation is the owner/assignee of USPN '130, rendering the instant application commonly owned/assigned in part with USPN '130. Thus, for the above reasons this rejection is proper.

The provisional rejection of claims 1, 8, 11, 31, and 43 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825) **is maintained** for the reasons of record, which have been restated herein. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the cited claims are substantially overlapping in scope and mutually obvious. Independent claim 1 of copending '825 claims a method of administering an alkyl saccharide composition comprising administering at least one alkyl saccharide having an alkyl chain length from 12 to about 14 carbon atoms and at least one saccharide moiety with antibacterial activity, at least one therapeutic agent and at least one enhancing agent. The term alkyl saccharide reads on alkyl glycoside. Independent claim 1 of the instant application claims a surfactant composition comprising at least one alkyl glycoside and/or at least one saccharide alkyl ester that when admixed with a drug stabilizes the biological activity and increases the bioavailability of the drug. Saccharide alky ester reads on enhancer. It is obvious from the wording of claim 1 of the instant application that the surfactants are intended to be mixed with a drug. Therefore, claim 1 of the instant application is obviated by the composition utilized in claim 1 of copending '825. Independent claim 31 of the instant application claims a method of administering a drug composition comprising a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alky has from about 10 to about 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug. The term "delivered" reads on administering. Both claims 11 and 43 state that the surfactant composition of the instant application is formulated for mucosal delivery. Mucosal delivery reads on "transmucosal delivery." In conclusion, an ordinary skilled artisan would have concluded that claims 1, 8, 11, 31, and 43 of the instant application are prima facie obvious over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing (1) that the Examiner has failed to set forth a prima facie case of obviousness per Applicants' claim amendments and (2) Applicants have overcome the rejection by the filing of a terminal disclaimer.

The Examiner respectfully disagrees. Regarding (2), the terminal disclaimer filed on 8/13/07 was limited to U.S. Patent No. 5,661,130 and does not mention copending application 11/193,825. Regarding (1), the claims of copending '825 claim compositions comprising (i) an active agent selected from a group of 12 proteins, including exendin-4 and (ii) an alkyl saccharide (i.e. an alkyl glycoside) that is administered intranassally (see claim 12 of copending '825) and comprises alkyl groups consisting of 12 and 14 carbon atoms (see claim 13 of copending '825). Thus, the instant rejection remains proper.

Other Matter

It is noted that claim 13 recites that ***the surfactant*** is stable for at least six months from about 4-25 °C.

Conclusion

Claims 1 and 3-46 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H. Alstrum-Acevedo/
Patent Examiner
Technology Center 1600

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616

Notice of References Cited	Application/Control No. 11/127,786	Applicant(s)/Patent Under Reexamination MEEZAN ET AL.	
	Examiner JAMES H. ALSTRUM	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2003/0087820	05-2003	Young et al.	514/12
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

OIPE
AUG 13 2007
PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §1.97 and § 1.98, Applicants submit for consideration in the above-identified application these document listed on the attached Form PTO-1449. The Examiner is requested to make these documents of record.

08/15/2007 EHAILE1 00000056 11127786
02 FC:1806 180.00 OP

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Check number 586657 in the total amount of $755.00 is enclosed as payment for the three-month Extension of Time fee ($225.00), Terminal Disclaimer fee ($65.00) and Information Disclosure Statement fee ($180.00). No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 13, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1616

OIPE
AUG 13 2007
PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

/J.H.A.A./	AA	Birkett et al., "How Drugs are Cleared By the Liver," *Austra Prescr*, Vol. 13, No. 4, pp. 88-89, 1990.
/J.H.A.A./	AB	Birkett et al., "Bioavailability and First Pass Clearance," *Austra Prescr,* Vol. 14, pp. 14-16, 1991.

EXAMINER	DATE CONSIDERED
/James Alstrum Acevedo/	03/01/2008

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449

National Library of Medicine - Medical Subject Headings

2007 MeSH

MeSH Supplementary Concept Data

Return to Entry Page

Name of Substance	exenatide
Record Type	C
Registry Number	141732-76-5
CAS Type 1 Name	Exendin 4
Entry Term	AC 2993
Entry Term	AC 2993 LAR
Entry Term	Byetta
Entry Term	Ex4 peptide
Entry Term	exendin 4
Entry Term	exendin-4
Heading Mapped to	*Peptides
Heading Mapped to	*Venoms
Indexing Information	Lizards
Indexing Information	Venoms
Indexing Information	Glucagon-Like Peptide 1
Source	J Biol Chem 1992 Apr 15;267(11):7402-5
Pharm. Action	Hypoglycemic Agents
Frequency	328
Note	amino acid sequence given in first source; isolated from the venom of the lizard Heloderma suspectum; increases pancreatic acinar cAMP; identical to exendin-3 except that Gly(2)-Glu(3) replaces Ser(2)-Asp(3); exenatide is a synthetic version of exendin-4; has antidiabetic and antiobesity activities; binds to GLP-1 receptor
Date of Entry	19920510
Revision Date	20061227
Unique ID	C074031

Return to Entry Page Link to NLM Cataloging Classification

PALM INTRANET

Day : Monday
Date: 3/3/2008
Time: 01:04:36

Inventor Name Search

Enter the first few letters of the Inventor's Last Name.
Additionally, enter the first few letters of the Inventor's First name.

Last Name	First Name	
Maggio	Edward	Search

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     FILE 'MEDLINE' ENTERED AT 01:41:00 ON 03 MAR 2008

     FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL' ENTERED AT 01:41:12 ON 03 MAR
     2008

     FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL, REGISTRY' ENTERED AT 01:42:56
     ON 03 MAR 2008
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L3            81 S L2 NOT PD>20040914
L4            15 S L3 AND (SURFACTANT OR (SURFACE(W)ACTIVE(W)AGENT))
L5            13 DUP REM L4 (2 DUPLICATES REMOVED)
L6            13 FOCUS L5 1-

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                 (EX4(2A) PEPTIDE) OR (EXENDIN(3A) 4) OR 141732-76-5/RN)


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L2           435 SEA L1 (P) (ORAL? OR NASAL? OR NASOLACRIMAL OR PULMONARY OR
                 INHALATION OR OCULAR?)


=> d L6 1-4 TI AB IBIB

L6   ANSWER 1 OF 13  USPATFULL on STN
TI     Novel exendin agonist formulations and methods of administration thereof
AB     Novel exendin and exendin agonist compound formulations and dosages and
       methods of administration thereof are provided. These compositions and
       methods are useful in treating diabetes and conditions that would be
       benefited by lowering plasma glucose or delaying and/or slowing gastric
       emptying or inhibiting food intake.
ACCESSION NUMBER:       2003:127605  USPATFULL
TITLE:                  Novel exendin agonist formulations and methods of
                        administration thereof
INVENTOR(S):            Young, Andrew A., La Jolla, CA, UNITED STATES
                        Kolterman, Orville G., Poway, CA, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2003087820      A1   20030508
APPLICATION INFO.:      US 2002-157224     A1   20020528  (10)
RELATED APPLN. INFO.:   Continuation-in-part of Ser. No. US 2001-889330, filed
                        on 27 Dec 2001, PENDING A 371 of International Ser. No.
                        WO 2000-US902, filed on 14 Jan 2000, PENDING

                               NUMBER        DATE
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PRIORITY INFORMATION:   US 1999-116380P    19990114 (60)
                        US 2000-175365P    20000110 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   Molly A. Holman, Ph.D., Amylin Pharmaceuticals, Inc.,
                        9373 Towne Centre Drive, San Diego, CA, 92121
NUMBER OF CLAIMS:       40
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EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 3512
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN
TI Protein powder for pulmonary delivery
AB This invention provides particles of a therapeutic protein core coated with a surfactant that are suitable for pulmonary delivery to the deep lung of a patient in need thereof. Spray drying processes for preparing powders of the core protein particles and powders of the respirable, surfactant-coated, therapeutic protein particles are provided. For example, insulin/DPPC (10:90) powder was prepared by spray drying using ethanol as a solvent. The spray-dried product was collected in 65.9% yield. The spray-dried DPPC-coated insulin powder showed prolonged time action in lowering blood glucose when administered by insufflation to rats.
ACCESSION NUMBER: 2001:903796 CAPLUS
DOCUMENT NUMBER: 136:25119
TITLE: Protein powder for pulmonary delivery
INVENTOR(S): Bhat, Meenakshi Ganapati; Cuff, George William; Wolff, Ronald Keith
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001093837	A2	20011213	WO 2001-US16472	20010531
WO 2001093837	A3	20020502		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2000-210423P P 20000608

L6 ANSWER 3 OF 13 USPATFULL on STN
TI DERIVATIVES OF GLP-1 ANALOGS
AB The present invention relates to a pharmaceutical composition comprising a GLP-1 derivative having a lipophilic substituent; and a surfactant.
ACCESSION NUMBER: 2001:123563 USPATFULL
TITLE: DERIVATIVES OF GLP-1 ANALOGS
INVENTOR(S): KNUDSEN, LISELOTTE BJERRE, VALBY, Denmark
HUUSFELDT, PER OLAF, KOBENHAVN K, Denmark
NIELSEN, PER FRANKLIN, VARLOSE, Denmark
KAARSHOLM, NIELS C., VANLOSE, Denmark
OLSEN, HELLE BIRK, ALLEROD, Denmark
BJORN, SOREN ERIK, LYNGBY, Denmark
PEDERSEN, FREDDY ZIMMERDAHL, VARLOSE, Denmark
MADSEN, KJELD, VARLOSE, Denmark

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011071	A1	20010802
	US 6458924	B2	20021001
APPLICATION INFO.:	US 1999-398111	A1	19990916 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-265141, filed on 8 Mar 1999, PENDING Continuation-in-part of Ser. No. US 1999-258750, filed on 26 Feb 1999, PENDING Continuation-in-part of Ser. No. US 1998-38432, filed on 11 Mar 1998, ABANDONED Continuation-in-part of Ser. No. US 1997-918810, filed on 26 Aug 1997, ABANDONED A 371 of International Ser. No. WO 1997-DK340, filed on 22 Aug 1997, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1996-931	19960830
	DK 1996-1259	19961108
	DK 1996-1470	19961220
	DK 1998-263	19980227
	DK 1998-264	19980227
	DK 1998-268	19980227
	EP 1998-610006	19980313
	DK 1998-507	19980408
	DK 1998-272	19980227
	DK 1998-274	19980227
	DK 1998-508	19980408
	DK 1998-509	19980408
	US 1997-35904P	19970124 (60)
	US 1997-36226P	19970125 (60)
	US 1997-36255P	19970124 (60)
	US 1998-78422P	19980318 (60)
	US 1998-82478P	19980421 (60)
	US 1998-82479P	19980421 (60)
	US 1998-82480P	19980421 (60)
	US 1998-82802P	19980423 (60)
	US 1998-84357P	19980505 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEVE T ZELSON, NOVO NORDISK OF NORTH AMERICA INC, 405 LEXINGTON AVENUE, SUITE 6400, NEW YORK, NY, 101746401
NUMBER OF CLAIMS: 238
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 15340
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 13 USPATFULL on STN
TI Use of exendins and agonists thereof for modulation of triglyceride levels and treatment of dyslipidemia
AB Methods for modulating the levels of plasma triglyceride and other lipids in a subject which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that lower blood triglyceride and/or other lipid levels.
ACCESSION NUMBER: 2003:51546 USPATFULL
TITLE: Use of exendins and agonists thereof for modulation of triglyceride levels and treatment of dyslipidemia
INVENTOR(S): Kolterman, Orville G., Poway, CA, UNITED STATES
Young, Andrew A., Point Loma, CA, UNITED STATES
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003036504	A1	20030220
APPLICATION INFO.:	US 2001-756690	A1	20010109 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-175365P	20000110 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BROBECK, PHLEGER & HARRISON LLP, 12390 EL CAMINO REAL, SAN DIEGO, CA, 92130
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 5350
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PALM INTRANET

Day : Monday
Date: 3/3/2008
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Inventor Name Search

Enter the first few letters of the Inventor's Last Name.
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Meezan	Elias	Search

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IBM Technical Disclosure Bulletins

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L10	L9 same surfactant	10	L10
L9	L1 same (insulin or glucagon)	916	L9
L8	L1 same (insulin or calcitonin or glucagon)	919	L8
L7	L3 and @ad<20040825	0	L7
L6	L5 and @ad<20040825	1	L6
L5	L4 NOT L3	6	L5
L4	L1 and L2	13	L4
L3	L1 same L2	7	L3
L2	("alkyl glycoside" or "saccharide alkyl ester" or TDM or tetradecylmaltoside or DDM or dodecylmaltoside)	35159	L2
L1	("Exendin 4" or "AC 2993" or "AC 2993 LAR" or byetta or "exendin 4")	1248	L1

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Refine Search

Search Results -

Terms	Documents
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EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L3

Refine Search

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Search History

DATE: Monday, March 03, 2008 Purge Queries Printable Copy Create Case

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L3	((((Edward near4 Maggio) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210	0	L3
L2	((((Dennis near4 Pillion) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210	0	L2
L1	((((Elias near Meezan) AND @pd>20070201) AND @pd>20070907) AND @pd>20071028) AND @pd>20080210	0	L1

END OF SEARCH HISTORY

```
     (FILE 'HOME' ENTERED AT 01:18:58 ON 03 MAR 2008)

     FILE 'CAPLUS, MEDLINE, USPATFULL' ENTERED AT 01:19:37 ON 03 MAR 2008
L1        26609 S ((ALKYL(2A)GLYCOSIDE) OR TDM OR DDM OR TETRADECYLMALTOSIDE OR
L2            7 S L1 (P) (EXENDIN OR EXENATIDE OR BYETTA OR (AC(W)2993) OR (EX4
L3            5 DUP REM L2 (2 DUPLICATES REMOVED)

=> d que L1
L1        26609 SEA ((ALKYL(2A) GLYCOSIDE) OR TDM OR DDM OR TETRADECYLMALTOSIDE
                 OR DODECYLMALTOSIDE OR (SACCHARIDE(3A) ESTER))


=> d que L2
L1        26609 SEA ((ALKYL(2A) GLYCOSIDE) OR TDM OR DDM OR TETRADECYLMALTOSIDE
                 OR DODECYLMALTOSIDE OR (SACCHARIDE(3A) ESTER))
L2            7 SEA L1 (P) (EXENDIN OR EXENATIDE OR BYETTA OR (AC(W) 2993) OR
                (EX4(W) PEPTIDE) OR (EXENDIN(3A) 4))


=> d L3 1-5 TI AB IBIB

L3   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2008 ACS on STN  DUPLICATE 1
TI   Antibacterial compositions comprising an alkyl glycoside
AB   An antibacterial composition having at least one alkyl glycoside, at least one
     saccharide, and at least one therapeutic agent is disclosed, wherein the
     alkyl glycoside has an alkyl chain length from about 12 to about 14 carbon
     atoms and wherein the saccharide has antibacterial activity.  Intranasal
     delivery and administration of the alkyl saccharide with drug results in
     lowering of blood glucose levels.
ACCESSION NUMBER:        2006:192153  CAPLUS
DOCUMENT NUMBER:         144:280575
TITLE:                   Antibacterial compositions comprising an alkyl
                         glycoside
INVENTOR(S):             Maggio, Edward T.
PATENT ASSIGNEE(S):      Aegis Therapeutics LLC, USA
SOURCE:                  U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S.
                         Ser. No. 127,786.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
     US 2006046969        A1    20060302    US 2005-193825          20050729
     US 2006046962        A1    20060302    US 2005-127786          20050511
     EP 1789075           A2    20070530    EP 2005-784486          20050511
         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
     IN 2007DN02126       A     20070803    IN 2007-DN2126          20070319
PRIORITY APPLN. INFO.:                      US 2004-604296P     P   20040825
                                            US 2004-609890P     P   20040914
                                            US 2004-632038P     P   20041130
                                            US 2004-637284P     P   20041217
                                            US 2005-649958P     P   20050203
                                            US 2005-127786      A2  20050511
                                            WO 2005-US16944     W   20050511

L3   ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2008 ACS on STN  DUPLICATE 2
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TI Alkyl glycoside absorption enhancers for drug administration

AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug is disclosed. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compns. that enhance absorption of drugs via the oral, ocular, nasal, inhalation or pulmonary, oral cavity (sublingual or buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and Exendin-4. Compns. consisting of alkyl glycosides, e.g., tetradecyl maltoside, plus insulin effectively lowered blood glucose levels, and that these effects are measurable shortly after administration of the drug.

ACCESSION NUMBER: 2006:191901 CAPLUS
DOCUMENT NUMBER: 144:260820
TITLE: Alkyl glycoside absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias; Pillion, Dennis J.; Maggio, Edward T.
PATENT ASSIGNEE(S): Aegis Therapeutics LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006046962	A1	20060302	US 2005-127786		20050511
WO 2006025882	A2	20060309	WO 2005-US16944		20050511
WO 2006025882	A3	20060810			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
EP 1789075	A2	20070530	EP 2005-784486		20050511
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
US 2006046969	A1	20060302	US 2005-193825		20050729
US 2006045868	A1	20060302	US 2005-202849		20050812
US 2006045869	A1	20060302	US 2005-219337		20050901
IN 2007DN02126	A	20070803	IN 2007-DN2126		20070319
PRIORITY APPLN. INFO.:			US 2004-604296P	P	20040825
			US 2004-609890P	P	20040914
			US 2004-632038P	P	20041130
			US 2004-637284P	P	20041217
			US 2005-649958P	P	20050203
			US 2005-127786	A2	20050511
			WO 2005-US16944	W	20050511

L3 ANSWER 3 OF 5 USPATFULL on STN

TI Vasoactive intestinal polypeptide pharmaceuticals

AB Pharmaceutical compositions relating to vasoactive intestinal

polypeptides and methods for the treatment of metabolic disorders, including diabetes, insulin resistance, metabolic acidosis and obesity are presented. Methods of using the vasoactive intestinal polypeptide compositions are also disclosed.

ACCESSION NUMBER: 2006:93325 USPATFULL
TITLE: Vasoactive intestinal polypeptide pharmaceuticals
INVENTOR(S): Nestor, John, Encinitas, CA, UNITED STATES
PATENT ASSIGNEE(S): Therapei Pharmaceuticals, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006079456	A1	20060413
APPLICATION INFO.:	US 2005-245499	A1	20051007 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-617500P	20041008 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WILSON SONSINI GOODRICH & ROSATI, 650 PAGE MILL ROAD, PALO ALTO, CA, 94304-1050, US
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1253
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 5 USPATFULL on STN
TI Absorption enhancers for drug administration
AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

ACCESSION NUMBER: 2006:53568 USPATFULL
TITLE: Absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias, Birmingham, AL, UNITED STATES
Pillion, Dennis J., Hoover, AL, UNITED STATES
Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): AEGIS THERAPEUTICS LLC (U.S. corporation)
THE UAB RESEARCH FOUNDATION (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006045869	A1	20060302
APPLICATION INFO.:	US 2005-219337	A1	20050901 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPER RUDNICK GRAY CARY US LLP, 4365 Executive Drive, Suite 1100, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1-86
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2029
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 5 USPATFULL on STN
TI Absorption enhancers for drug administration
AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.
ACCESSION NUMBER: 2006:53567 USPATFULL
TITLE: Absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias, Birmingham, AL, UNITED STATES
Pillion, Dennis J., Hoover, AL, UNITED STATES
Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): AEGIS THERAPEUTICS LLC (U.S. corporation)
THE UAB RESEARCH FOUNDATION (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006045868	A1	20060302
APPLICATION INFO.:	US 2005-202849	A1	20050812 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPER RUDNICK GRAY CARY US LLP, Suite 1100, 4365 Executive Drive, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1-46
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1964
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

Responsive to the Office Communication mailed November 2, 2007 and the Office Action mailed February 12, 2007, please amend the above-identified application as follows:

Amendments to the Specification are reflected beginning on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 7 of this paper.

Remarks/Arguments begin on page 14 of this paper.

Amendments to the Specification

Please replace paragraph [0025] of the specification with the following amended paragraph:

[0025] In one aspect, the invention provides a method of controlling caloric intake by administering a composition having a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of INTRAVAIL® ~~Intravail~~ alkyl saccharide.

Please replace paragraph [0026] of the specification with the following amended paragraph:

[0026] In another aspect, the invention provides a method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of INTRAVAIL® ~~Intravail~~ alkyl saccharide.

Please replace paragraph [0030] of the specification with the following amended paragraph:

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25% TDM and IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following IP injection ~~oral~~ administration of glucose (i.e., in a so-called "glucose tolerance test").

Please replace paragraph [0045] of the specification with the following amended paragraph:

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a hydrophilic ~~hydrophobic~~ saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

Please replace paragraph [0051] of the specification with the following amended paragraph:

[0051] Accordingly, a subject treated with surfactant compositions of the invention having at least one alkyl glycoside, e.g. tetradecylmaltoside (TDM; or INTRAVAIL® ~~Intravail~~ A), at a concentration of about 0.125% by weight of alkyl glycoside two times per day, or three times per day, or more depending on the treatment regimen consumes about 200 to 300 micrograms per day total of TDM. So, the effective dose of the TDM is at least 1000X fold lower than (i.e., 1/1000) of the NOAEL, and falls far below 1% of the NOAEL, which is the acceptable daily intake; or in this case about 1/50,000 of the acceptable daily intake.. Stated another way, alkyl glycosides of the present invention have a high NOAEL, such that the amount or concentration of alkyl glycosides used in the present invention do not cause an adverse effect and can be safely consumed without any adverse effect.

Please replace paragraph [0117] of the specification with the following amended paragraph:

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other ~~highly branched~~ long alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Please replace paragraph [0135] with the following amended paragraph:

[0135] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase in the blood glucose levels as shown in FIG. 2 (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhibition of pancreatic insulin secretion. Blood glucose levels peak to about 482 mg/dl by 30 minutes after the xylazine-ketamine injection (FIG. 2). Then, at approximately 33 minutes after the xylazine-ketamine injection, 6 μL of insulin

~~(Humalog)~~ (HUMALOG®) in 0.25% tetradecylmaltoside (TDM; or INTRAVAIL® ~~Intravail~~ A) was administered intranasally using a long thin micropipette tip, and blood glucose levels were monitored at about 15 minute intervals. After administration of the 0.25% TDM/insulin composition, there was a rapid decrease in blood glucose levels, reaching a low of about 80 mg/dl at about the 60 minute time point, or about 30 minutes after the insulin administration (FIG. 2). At about the 75 minute time point, blood glucose levels gradually returned to the baseline level in a normoglycemic mouse, or about 80-100 mg/dl.

Please replace Table 1 at p.44 with the following amended table:

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	~~144~~ 141 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

Please replace the header of Example 5 at page 47, with the following amended title:

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS GLUCAGON ~~INSULIN~~ PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

Amendments to the Claims

Please amend claims 1, 4-6, 12, 14-18, 20-31, 33-38, 40-42, and 44-46 as provided below.

Please cancel claim 2 without prejudice or disclaimer.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A surfactant composition comprising ~~of~~ at least one alkyl glycoside ~~and/~~or at least one saccharide alkyl ester~~, and when~~ admixed with a drug, wherein the surfactant maintains ~~stabilizes~~ the biological activity and increases the bioavailability, of the drug, wherein the drug is exendin-4.

2. (Canceled)

3. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. (Currently Amended) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than ~~the~~ an acceptable daily intake amount of the surfactant.

5. (Currently Amended) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than ~~the~~ an acceptable daily intake amount of the surfactant.

6. (Currently Amended) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 1000 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

7. (Original) The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. (Original) The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. (Original) The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. (Currently Amended) The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system of a subject.

13. (Original) The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. (Currently Amended) The composition of claim 1, wherein the surfactant is at a concentration ~~is from~~ of about 0.01% to 20% (w/v).

15. (Currently Amended) The composition of claim 1, wherein the surfactant ~~concentration~~ is at a concentration of ~~from~~ about 0.01% to 5% (w/v).

16. (Currently Amended) The composition of claim 1, wherein the surfactant is at a concentration of ~~is from~~ about 0.01% to 2% (w/v).

17. (Currently Amended) A therapeutic composition comprising ~~of~~ at least one ~~biologically active compound(s)~~ drug and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside ~~and/~~or saccharide alkyl ester and wherein said composition maintains ~~stabilizes~~ the biological activity of the drug, for at least about 6 months from about 4°C to 25°C, and wherein the drug is exendin-4.

18. (Currently Amended) The composition of claim 17, wherein ~~the pH of~~ the composition has a pH ~~is~~ less than 8.0.

19. (Original) The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. (Currently Amended) The composition of claim 17, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 20% (w/v).

21. (Currently Amended) The composition of claim 17, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 5% (w/v).

22. (Currently Amended) The composition of claim 17, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 2% (w/v).

23. (Currently Amended) ~~A stable~~ The therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. (Currently Amended) ~~A stable~~ The therapeutic composition according to claim 17, wherein ~~the~~ administration to a ~~the~~ subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of the ~~said~~ biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of the ~~said~~ subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or

blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the ~~said~~ subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to ~~the~~ a subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of the ~~said~~ biologically active compound(s) to the subject.

27. (Currently Amended) The therapeutic composition of claim 17, wherein said composition following mucosal administration to a ~~said~~ subject yields an area under

concentration curve (AUC) of the ~~said~~ biologically active compound(s) in the ~~said~~ CNS tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of the ~~said~~ biologically active compound(s) in the ~~said~~ CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of the ~~said~~ biologically active compound(s) to the ~~said~~ subject.

28. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields an area under concentration curve (AUC) of the ~~said~~ biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in the ~~said~~ CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. (Currently Amended) The therapeutic ~~pharmaceutical~~ composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. (Currently Amended) The ~~pharmaceutical~~ composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. (Currently Amended) A method of administering a drug composition comprising ~~of~~ a surfactant having at least one alkyl glycoside ~~and/~~or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the ~~stability and~~ bioavailability of the drug wherein the drug is exendin-4.

32. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

34. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

35. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

36. (Currently Amended) The method of claim 31, wherein the surfactant reduces variance in ~~the~~ bioavailability ~~variance~~ from patient to patient.

37. (Currently Amended) The method of claim 31, wherein the composition does not enter the hepatic portal blood system of a subject.

38. (Currently Amended) The method of claim 31, wherein ~~the pH of~~ the composition has a pH ~~is~~ less than 8.0.

39. (Original) The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. (Currently Amended) The method of claim 31, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 20% (w/v).

41. (Currently Amended) The method of claim 31, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 5% (w/v).

42. (Currently Amended) The method of claim 31, wherein the ~~composition~~ surfactant has a concentration of ~~is from~~ about 0.01% to 2% (w/v).

43. (Original) The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. (Currently Amended) The composition ~~method~~ of claim 1, wherein the composition ~~is~~ further comprises ~~comprised of~~ an enteric coating.

45. (Currently Amended) The composition ~~method~~ of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM) or dodecylmaltoside (DDM).

46. (Currently Amended) The composition ~~method~~ of claim 45, wherein the TDM or DDM has anti-bacterial activity.

47 to 138. (Canceled).

REMARKS

The remarks are in response to the Office Communication dated November 2, 2007 and the Office Action dated February 12, 2007. Claims 1, 4-6, 12, 14-18, 20-31, 33-38, 40-42, and 44-46 have been amended. Claim 2 is canceled without prejudice or disclaimer. Claims 47-138 were previously canceled without prejudice. Subsequent to the entry of the present amendment, claims 1 and 3-46 will be pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

Information Disclosure Statement

The Office Action alleges that the manuscripts listed in paragraph [0141] fail to comply with the provisions of 37 C.F.R §§1.98(b) because the references were not submitted in a separate paper and may not be incorporated into the specification. Applicants respectfully submit that four of the articles cited by the Examiner, provided below, were previously submitted in an information disclosure statement filed on October, 31 2005. Accordingly, Applicants respectfully request withdrawal of the Examiner's objection with regard to the references.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132:107-113.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides. B. Oral absorption *in vivo* in rats," *Int. J. Pharmaceutics* 132:115-121.

Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213.

The Office Action also alleges that two additional manuscripts included in paragraph [0141] fail to comply with the provisions of 37 C.F.R §§1.98(b) because the references were not submitted in a separate paper and may not be incorporated into the specification. Attached herewith is a submission of an IDS on a form PTO/SB/08 1449 for consideration by the Examiner. Applicants respectfully request withdrawal of the objection.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 17-46 are rejected under 35 U.S.C. §112, for allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

It is well-established that an "objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). *Under Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed". See MPEP §2163.04.

Applicants respectfully submit that support for claims 17-46 can be found in, for example, paragraph [0048] and [0049] of the specification as filed. Further, in view of the art known at the time of filing, Applicants submit that the specification, as filed, conveys with reasonable clarity that the Applicants were in possession of the claimed invention as of the filing date.

For example, the present specification highlights U.S. Patent No. 5,726,154 (hereafter "the '154 patent"), which is incorporated by reference in its entirety, which describes characteristics of similar therapeutic compositions to those claimed in the present invention. The '154 patent describes aqueous mixtures of an effective amount of a surfactant (SDS) and an effective amount of organic acid in order to provide storage of calcitonin for up to 6 months at

between 4°C - 25°C (see, e.g., Tables 1 and 2, columns 5 and 6 respectively of the '154 patent). Applicants submit that the '154 patent establishes the state of the art at the time the application was filed and that the present invention amply demonstrates the Applicants were in possession of the invention at the time of filing. (see for example, claim 13 and paragraph [0006] of the specification as filed). The specification at Paragragh [0048] states:

> The surfactant compositions of the invention are stable. For example, Baudys et al. in U.S. Patent No. 5,726,154 show that calcitonin in an aqueous liquid composition comprising SDS (sodium dodecyl sulfate, a surfactant) and an organic acid is stable for at least 6 months. Similarly, the surfactant compositions of the present invention have improved stabilizing characteristics when admixed with a drug. No organic acid is required in these formulations. For example, the composition of the invention maintains the stability of proteins and peptide therapeutics for about 6 months, or more, when maintained at about 4°C to 25°C.

Applicants further submit that the bioavailability data presented in, for example, Figure 1, Figure 3 and paragraphs [0117] and [0118], allow the skilled artisan to extrapolate pharmacokinetic parameters such as, for example, C_{max} and AUC for exendin-4 containing compositions. Thus, Applicants respectfully submit that the specification clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date, the Applicants were in possession of the claimed invention.

Accordingly, withdrawal of rejection of claims 17-46 under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 31-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office indicates that the claims are enabling for methods of administering a drug composition including exendin-4. Without acquiescing to the reasoning of the Office, and in

order to expedite prosecution of the instant application, Applicants have amended claim 31 to recite "wherein the drug is exendin-4." The Office alleges that while exendin-4 is enabled, it is allegedly only enabled in combination with an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside with specific administration routes.

Applicants respectfully submit that the specification provides sufficient guidance to allow one skilled in the art to make or use the invention commensurate in scope with the claims as amended. Contrary to the assertion of the Office, Applicants respectfully submit that one of skill in that art would be capable of generating formulations of exendin-4 with a host of alkyl glycosides or saccharide alkyl esters for delivery via a host of routes without having to undertake undue experimentation. The specification abundantly teaches which surfactants may be used along with methods of synthesis (see, for example, the specification, paragraphs [0041]-[0048], the preferred concentrations of surfactant and drug (see, for example, the specification, paragraphs [0051]), and working examples with exendin-4 (see for example the specification, Example 7 and Figure 3).

Applicants point out that routine experimentation does not constitute undue experimentation. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine..." (see *Johns Hopkins University v. Cellpro, Inc.*, 47 USPQ2d 1705 (Fed. Cir. 1998)). The fact that experimentation may be complex does not necessarily make it undue (see *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985)). As discussed above, the specification provides ample guidance as to different surfactants, formulations and delivery routes. The Examiner admits that the relative skill of an artisan in the field to which the invention pertains is high (Office Action, page 9, paragraph 1). As such, Applicants submit that it would be routine experimentation for one skilled in the art to prepare compositions including exendin-4 in combination with an alkyl glycoside or saccharide alkyl ester for delivery to a subject via various routes.

The Office further alleges that that prior art recognizes that only some alkyl glycosides are characterized by the ability to enhance penetration of drugs across mucosal epithelia and thereby the bioavailability of a drug. Applicants respectfully submit that the specification is enabled as acknowledged by the Office and that Applicants are not required to show that every possible alkyl glycoside is operable because under 35 U.S.C. §112, first paragraph, the specification and claims may include inoperative examples where guidance and operative embodiments are provided (see, *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.,* 224 USPQ 409 (Fed. Cir. 1984)). Furthermore, it is not the function of the claims to exclude possible inoperative inventions (*Id.*).

Accordingly, withdrawal of rejection of claims 31-46 under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claims 2, 4-6, and 14-46 are rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims. Applicants have canceled claim 2, rendering the rejection moot as to claim 2.

Claims 4-6, 12, 14-16, 17, 18, 21-22, 24, 25-30, 37, 38 and 40-42 are rejected for reciting a claim limitation for which there is allegedly insufficient antecedent basis. Applicants have amended the claims and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that it appears that the Examiner's rejection of claim 24, as allegedly reciting a claim limitation for which there is allegedly insufficient antecedent basis, should be directed to claim 36. Applicants have amended claim 36 and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim 31 is rejected for allegedly being vague and indefinite. Applicants have amended claim 31 and respectfully submit that the claim as amended renders the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 14-16 are rejected for allegedly being confusing and indefinite because the claims only require the composition to include a surfactant but recite a surfactant composition other than 100%. Applicants respectfully submit that the composition of claim 1, from which claims 14-16 comprises a surfactant and a drug. As such, it is clear that the composition may include additional components wherein the surfactant concentration may be as recited in claims 14-16. For clarity, Applicants have amended claims 14-16 to emphasize that the concentration of surfactant is 0.01% to 20% (w/v), 0.01% to 5% (w/v) and 0.01% to 2% (w/v) respectively. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 20-22 and 40-42 are rejected as allegedly being confusing and indefinite because they claim a therapeutic composition and also refer to a composition concentration that is less than 100%. Applicants have amended the claims to recite "wherein the surfactant has a concentration" and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 44-45 are rejected as allegedly being vague and indefinite for referring to a method while depending on claim 1 which recites a composition. Applicants have amended claims 44-45 to recite the "composition of claim 1" and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Office Action also alleges that claims 3-6 and 32-35 contain the indefinite term "high". Applicants direct the Examiner's attention to paragraphs [0049], [0050] and [0051] wherein the term "high" is described with sufficient clarity to convey to the skilled artisan the meaning of the term as it pertains to NOAEL. Applicants therefore, submit that the skilled artisan would understand the term "high" as it pertains to (NOAEL). Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 14-16, 20-22 and 40-42 are rejected for allegedly being vague and indefinite for not reciting units of measure. Applicants have amended the claims and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim 12 is rejected for allegedly being vague and indefinite because the claimed composition allegedly does not comprise a drug. Applicants have amended claim 1, from which claim 12 depends to recite a drug and respectfully submit that the claims as amended render the rejection moot. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. §102

Claims 1-13, 17-19, 23-36, 38-39 and 43 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Hovgaard et al. (hereinafter, "Hovgaard"). Applicants respectfully traverse the rejection as it applies to the pending claims.

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference, and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

Applicants respectfully submit that Hovgaard does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Hoovgard does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-17 and 19-30 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Watanabe et al. (hereinafter, "Watanabe"). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Watanabe does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Watanabe does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-30 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Sekiguchi et al. (hereinafter, "Sekiguchi", U.S. Patent No. 5,109,127). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Sekiguchi does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Sekiguchi does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-43 and 45-46 are rejected under §102(b) as allegedly anticipated by Kee et al. (hereinafter, "Kee", U.S. Patent No. 5,369,095). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Kee does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Kee does not teach or disclose a composition including exendin-4 and thus fails to

teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-10 and 12-13 are rejected under §102(b) as allegedly anticipated by Lamberti et al. (hereinafter, "Lamberti", U.S. Patent No. 3,849,341). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Lamberti does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Lamberti does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-7 and 9-14 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Koike et al. (hereinafter, "Koike" U.S. Patent No. 5,639,733). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Koike does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Koike does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-43 and 45-46 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meezan et al. (hereinafter, "Meezan '130" U.S. Patent No. 5,661,130). Applicants respectfully traverse the rejection as it applies to the pending claims. The Office Action alleges that Meezan

discloses preferred glycosides including maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12 or 14 carbon atoms.

Applicants respectfully submit that Meezan '130 does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Meezan '130 does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-13, 17-19, 23-27, 39, 43 and 45-46 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meezan et al. (hereinafter, "Meezan '634" U.S. Patent No. 5,817,634). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that Meezan '634 does not anticipate the claims as amended because the reference does not teach each and every element of the amended claims. Applicants have amended the claims to recite "wherein the drug is exendin-4". Applicants respectfully submit that Meezan '634 does not teach or disclose a composition including exendin-4 and thus fails to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-13 and 45-46 are rejected under 35 U.S.C. §102(f) because the Examiner alleges that Applicants did not invent the claimed subject matter. Applicants respectfully traverse the rejection as it applies to the pending claims.

Without acquiescing to the Office's reasoning, claim 1 has been amended to recite a surfactant composition admixed *with* exendin-4, thus, the rejection no longer applies. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1-46 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter "the '130 Patent") in view of Crotts et al. (US 2003/0017203; hereinafter "Crotts"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The recent U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

With regard to amended claims 1-16, the Office alleges that the '130 Patent discloses compositions including glycosides to enhance the absorption of peptide hormones. Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, with respect to the amended claims, because the Office has failed to show some suggestion or motivation to modify a reference or to combine the teachings of multiple references. Independent claim 1 has been amended to include exendin-4, which was not disclosed in the '130 Patent. Additionally, claim 1 includes the proviso that the surfactant maintains the biological activity and increases the bioavailability of the drug. Applicants respectfully submit that the '130 patent is silent as to maintaining biological activity of exendin-4. Therefore, Applicants respectfully submit that based on the teachings of the '130 Patent, one of skill in the art would not have been motivated to modify the teachings of the '130 Patent to obtain a composition including previously undisclosed exendin-4 or with the properties as claimed. It would not have been obvious for one of skill in the art that such embodiments would be possible.

Even if one were to modify the '130 Patent, there is no *prima facie* case of obviousness as to the amended claims, because the reference does not teach each and every element of the claimed invention. The '130 Patent fails to teach exendin-4 in combination with a surfactant that is an alkyl glycoside or saccharide alkyl ester in which the activity of the drug is maintained.

With regard to amended claims 44-46, directed to a composition including exendin-4 and an enteric coating, the Office alleges that Crotts cures the lack of teaching an enteric coating in the '130 Patent because it describes compositions as absorption enhancers which may allegedly be comprised of any peptide that is useful in the treatment of a disease or condition. However, as discussed above Crotts fails to teach or suggest compositions including exendin-4 with the specified *in vivo* character of the present invention and also fails to describe compounds which exhibit the claimed stability.

With regard to amended claims 17-43, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because the Office has failed to show some suggestion or motivation to modify a reference or to combine the teachings of multiple references. Independent claims 17 and 31 have been amended to include exendin-4 which was not disclosed in the '130 Patent. Additionally, claims 17 and 31 include the provisos that the surfactant maintains the biological activity of exendin-4 for at least 6 months from about 4°C to 25°C and the surfactant increases the bioavailability of exendin-4, respectively. The specification at paragraph [0049] teaches that the stability of the formulation of the present invention are increased due to the high no observable adverse effect level (NOAEL). Additionally, the specification teaches the increased bioavailability of the compositions (see, for example, the specification, Figures 1 and 3, and Example 7). Therefore, Applicants respectfully submit that based on the teachings of the '130 Patent, one of skill in the art would not have been motivated to modify the teachings of the '130 Patent to obtain a composition including previously undisclosed exendin-4 or to provide a method of delivery of a composition including

exendin-4 along with a surfactant with increased stability and bioavailability. It would not have been obvious for one of skill in the art that such embodiments would be possible.

Accordingly, because the Office has failed to establish a *prima facie* case of obviousness, Applicants respectfully request the rejection on the ground of nonstatutory obviousness-type double patenting over the '130 Patent be withdrawn.

Rejections Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Applicants request the following remarks be considered along with the arguments presented immediately below. In the Office Action mailed February 12, 2007, the Office rejected claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 under the judicially created doctrine of obviousness double patenting allegedly over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (hereafter "the '130 Patent"). Applicants subsequently filed a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) (with respect to the '130 Patent) along with the Amendment filed August 13, 2007 in response to the Office Action, to overcome the rejection. Applicants respectfully request that the Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) (with respect to the '130 Patent) be withdrawn and the arguments presented below in opposition to the rejection be entered.

A proper nonstatutory obviousness-type double patenting rejection requires two or more patents or applications to have at least one common inventor and be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement (see MPEP 804). Under 37 C.F.R. §1.321(c), a terminal disclaimer may be filed to obviate a double patenting rejection where the cited patent and application are commonly owned. Applicants respectfully submit that where the cited patent and pending application are not commonly owned, and the rejection results from activities undertaken within the scope of a joint research agreement, a terminal disclaimer may be filed under 37 C.F.R. §1.321(d) to obviate the rejection.

Applicants respectfully submit that the present application, U.S. Patent Application Serial No. 11/127,786 (hereafter "the '786 Application") was made as a result of activities undertaken

within the scope of a joint research agreement. Furthermore, the subject matter of the '786 Application complies with the provisions of the Cooperative Research and Technology Enhancement Act (CREATE Act) of 2004, 35 U.S.C. §103(c)(2), 37 C.F.R., Parts 1 and 3 (effective September 14, 2005) with respect to the '130 Patent.

Additionally, the '786 Application does not share common ownership with the '130 Patent. Pursuant to an obligation to assign, Dr. Elias Meezan and Dr. Dennis Pillion assigned their rights in the present application (Application Serial No. 11/127,786, filed May 11, 2005, "the '786 Application") to The UAB Research Foundation (recorded August 2, 2005, at Reel 016343, Frame 0736) and Dr. Edward Maggio assigned his rights to Aegis Therapeutics L.L.C. (recorded May 23, 2005, at Reel 016052, Frame 0555). Further pursuant to an obligation to assign Dr. Elias Meezan and Dr. Dennis Pillion assigned their right in the '130 Patent to The UAB Research Foundation (recorded August 2, 1993, at Reel 006631, Frame 0968).

Accordingly, because the '786 Application was made as a result of activities undertaken within the scope of a joint research agreement but does not share common ownership with the '130 Patent, the Terminal Disclaimer filed on August 13, 2007, in compliance with 37 C.F.R. §1.321(c) is invalid. Therefore, Applicants request that the Terminal Disclaimer filed to overcome the nonstatutory obviousness-type double patenting rejection based on the '130 Patent be withdrawn and the arguments presented below in opposition to the rejection be entered.

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 are rejected under the judicially created doctrine of obviousness double patenting allegedly over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (hereafter "the '130 Patent"). Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons previously presented above in response to the 35 U.S.C. §103(a) rejection.

With regard to amended claims 1-16 and 45-46, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, with respect to the amended claims, because the Office has failed to show some suggestion or motivation to modify a

reference or to combine the teachings of multiple references. Independent claim 1 has been amended to include exendin-4, which was not disclosed in the '130 Patent. Additionally, claim 1 includes the proviso that the surfactant maintains the biological activity and increases the bioavailability of the drug. Applicants respectfully submit that the '130 patent is silent as to maintaining biological activity of exendin-4. Therefore, Applicants respectfully submit that based on the teachings of the '130 Patent, one of skill in the art would not have been motivated to modify the teachings of the '130 Patent to obtain a composition including previously undisclosed exendin-4 or with the properties as claimed. It would not have been obvious for one of skill in the art that such embodiments would be possible.

Even if one were to modify the '130 Patent, there is no *prima facie* case of obviousness as to the amended claims, because the reference does not teach each and every element of the claimed invention. The '130 Patent fails to teach exendin-4 in combination with a surfactant that is an alkyl glycoside or saccharide alkyl ester in which the activity of the drug is maintained.

With regard to amended claims 17-43, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because the Office has failed to show some suggestion or motivation to modify a reference or to combine the teachings of multiple references. Independent claims 17 and 31 have been amended to include exendin-4 which was not disclosed in the '130 Patent. Additionally, claims 17 and 31 include the provisos that the surfactant maintains the biological activity of exendin-4 for at least 6 months from about 4°C to 25°C and the surfactant increases the bioavailability of exendin-4, respectively. The specification at paragraph [0049] teaches that the stability of the formulation of the present invention are increased due to the high no observable adverse effect level (NOAEL). Additionally, the specification teaches the increased bioavailability of the compositions (see, for example, the specification, Figures 1 and 3, and Example 7). Therefore, Applicants respectfully submit that based on the teachings of the '130 Patent, one of skill in the art would not have been motivated to modify the teachings of the '130 Patent to obtain a composition including previously undisclosed exendin-4 or to provide a method of delivery of a composition including

exendin-4 along with a surfactant with increased stability and bioavailability. It would not have been obvious for one of skill in the art that such embodiments would be possible.

Accordingly, because the Office has failed to establish a *prima facie* case of obviousness, Applicants respectfully request the rejection on the ground of nonstatutory obviousness-type double patenting over the '130 Patent be withdrawn.

Claims 1, 8, 11, 31 and 43 are rejected under the judicially created doctrine of obviousness double patenting, allegedly over claims 1-6 and 12-13 of co-pending U.S. Application No. 11/193,825 (hereafter '825). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that claims 1, 17, 31 and 45 have been amended in order to add particularity in distinguishing the present invention from the '825 application, thus the rejection, as it pertains to these claims, no longer applies. Accordingly, Applicants assert that the Examiner has failed to meet his burden of demonstrating a *prima facia* case of obviousness and withdrawal of the rejection as they apply to the pending claims is respectfully requested.

Without acquiescing to the Office's reasoning, and in the interest of advancing prosecution in this case, Applicants submit herewith a terminal disclaimer. Thus, the rejection no longer applies to the pending claims and withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of $60.00 as payment for the One-Month Extension of Time fee to Deposit Account No.: 07-1896. No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: December 14, 2007

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) AEGIS1210
Application Number 11/127,786	Filed May 11, 2005
For ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION	
Art Unit 1616	Examiner J.H. ALSTRUM ACEVEDO

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☒	One month (37 CFR 1.17(a)(1))	$120	$60	$ 60.00
☐	Two months (37 CFR 1.17(a)(2))	$460	$230	$
☐	Three months (37 CFR 1.17(a)(3))	$1050	$525	$
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 07-1896 referencing the attorney docket number identified above.

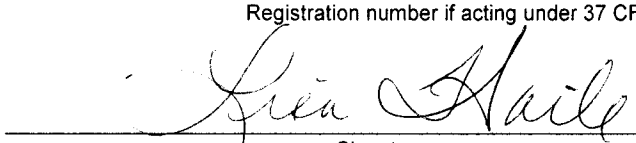
WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 38,347

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____.



Signature — December 14, 2007 (Date)

LISA A. HAILE, J.D., Ph.D. (Typed or printed name) — (858) 677-1456 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms is submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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356894-12

Electronic Patent Application Fee Transmittal

Application Number:	11127786
Filing Date:	11-May-2005
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Filer:	Lisa A. Haile/Karen LePari
Attorney Docket Number:	AEGIS1210

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	60	60

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**60**

Electronic Acknowledgement Receipt

EFS ID:	2595716
Application Number:	11127786
International Application Number:	
Confirmation Number:	5393
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Customer Number:	28213
Filer:	Lisa A. Haile/Karen LePari
Filer Authorized By:	Lisa A. Haile
Attorney Docket Number:	AEGIS1210
Receipt Date:	14-DEC-2007
Filing Date:	11-MAY-2005
Time Stamp:	18:34:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$60
RAM confirmation Number	3065
Deposit Account	071896
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		AEGIS1210.pdf	1415441 5a7a1f9544a84f627430961b30d7011ef1f4f4842	yes	33

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Miscellaneous Incoming Letter	1	2
Amendment - After Non-Final Rejection	3	32
Extension of Time	33	33

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	8140 8edc73f6502c28d074a74bcc923fbb80446e1dcf	no	2

Warnings:

Information:

Total Files Size (in bytes):	1423581

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Amendment (30 pages) and
2. One-Month Petition for Extension of Time (1 page).

GT\6554839.1
356894-12

The Commissioner is hereby authorized to charge the total amount of $60.00 as payment for the One-Month Extension of Time fee to Deposit Account No.: 07-1896. No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: December 14, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO Customer No. 28213

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,786	05/11/2005	Elias Meczan	AEGIS1210	5393

28213 7590 11/02/2007

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on *13 August 2007* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☒ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *See Continuation Sheet*.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

_____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

SABIHA QAZI, PH.D
PRIMARY EXAMINER

Legal Instruments Examiner (LIE), if applicable | Telephone No.

U.S. Patent and Trademark Office | Part of Paper No. 20071028b

Continuation of 4(e) Other: Applicants have indicated that claim 2 is currently withdrawn from consideration, which is incorrect. Claim 2 is not subject to a restriction requirement or species election. In fact, there is no restriction or species election requirement of record. Thus, the indicated claim identifier is mistaken and appropriate correction is required.

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Declaration under 37 C.F.R. §1.132 (3 pgs.).

GT\6546121.1
356894-12

Please note, the Declaration under 37 C.F.R. §1.132, was previously filed with the Response to Office Action mailed February 12, 2007 and filed on August 13, 2007. The Declaration was executed by two of the three inventors; Drs. Meezan and Maggio. The third inventor in this matter, Dr. Pillion, was previously unable to execute the Declaration. To complete the Declaration for this matter, attached herewith is Dr. Pillion's signature.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: September 27, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

We, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio declare and state that:

1. We are co-inventors of the subject matter described and claimed in the U.S. Patent Application Serial No. 11/127,786, filed on May 11, 2005, entitled, "ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION", which claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now abandoned; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now abandoned.

2. We are familiar with the prosecution history of U.S. Patent Application Serial No. 11/127,786.

3. We understand that the Examiner rejected claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 under the judicially created doctrine of obviousness double patenting allegedly over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130.

4. We attest that the present invention does not share common ownership with U.S. Patent No. 5,661,130 and that Dr. Edward T. Maggio has currently assigned his rights in the present application to Aegis Therapeutics, LLC and Dr. Elias Meezan and Dr. Dennis J. Pillion have assigned their rights in the present application to the UAB Research Foundation.

5. We attest that the subject matter of U.S. Patent Application Serial No. 11/127,786 complies with the provisions of the Cooperative Research and Technology Enhancement Act (CREATE) of 2004, 35 U.S.C. §103(c)(2), 37 C.F.R. Parts 1 and 3 (Effective date September 14, 2005) and further attest that all requirements of the Act, as it pertains to the present case, are hereby met.

6. We attest that the present invention was made as a result of activities undertaken within the scope of a joint research agreement and further declare, that the application as filed, discloses the proper names of the parties to the joint research agreement.

7. We attest that an amendment to the specification adding the names of the parties to the joint agreement, pursuant to the CREATE Act provisions, is not required, since the application as filed, discloses the requisite parties, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio.

8. We declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

9/25/07
Date

Dr. Elias Meezan

9/25/07
Date

Dr. Dennis J. Pillion

Date

Dr. Edward Maggio

Electronic Acknowledgement Receipt

EFS ID:	2252011
Application Number:	11127786
International Application Number:	
Confirmation Number:	5393
Title of Invention:	Absorption enhancers for drug administration
First Named Inventor/Applicant Name:	Elias Meezan
Customer Number:	28213
Filer:	Lisa A. Haile/Karen LePari
Filer Authorized By:	Lisa A. Haile
Attorney Docket Number:	AEGIS1210
Receipt Date:	27-SEP-2007
Filing Date:	11-MAY-2005
Time Stamp:	17:39:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		Document.pdf	155106 32dfed3979db772f0dcf1c03ada4388ff12160ea	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	2
	Rule 130, 131 or 132 Affidavits	3	5
Warnings:			
Information:			
	Total Files Size (in bytes):	155106	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Declaration under 37 C.F.R. §1.132 (3 pgs.).

GT\6546121.1
356894-12

Please note, the Declaration under 37 C.F.R. §1.132, was previously filed with the Response to Office Action mailed February 12, 2007 and filed on August 13, 2007. The Declaration was executed by two of the three inventors; Drs. Meezan and Maggio. The third inventor in this matter, Dr. Pillion, was previously unable to execute the Declaration. To complete the Declaration for this matter, attached herewith is Dr. Pillion's signature.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: September 27, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/127,786	MEEZAN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 13 Aug. 2007	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Dorethea Lawrence

U.S. Patent and Trademark Office

OIPE IAP66
AUG 13 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §1.97 and § 1.98, Applicants submit for consideration in the above-identified application these document listed on the attached Form PTO-1449. The Examiner is requested to make these documents of record.

08/15/2007 EHAILE1 00000056 11127786
02 FC:1806 180.00 OP

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"EXPRESS MAIL" LABEL NUMBER **EM 023 788 864 US** DATE OF DEPOSIT **August 13, 2007**

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450 , ALEXANDRIA, VA 22313-1450.

Tim Lasher
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER)

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

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356894-12

Check number 586657 in the total amount of $755.00 is enclosed as payment for the three-month Extension of Time fee ($225.00), Terminal Disclaimer fee ($65.00) and Information Disclosure Statement fee ($180.00). No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 13, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1616

OPE 1996
AUG 13 2007
PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

	AA	Birkett et al., "How Drugs are Cleared By the Liver," *Austra Prescr*, Vol. 13, No. 4, pp. 88-89, 1990.
	AB	Birkett et al., "Bioavailability and First Pass Clearance," *Austra Prescr,* Vol. 14, pp. 14-16, 1991.

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449

08-15-07

LFW



PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Amendment (28 pgs.);
2. Three-Month Petition for Extension of Time (1 pg., in dup.);
3. Replacement Drawings (3 sheets);
4. Information Disclosure Statement (2 pgs.);
5. Form PTO-1449 (1 pg.);
6. Two References;
7. Terminal Disclaimer (3 pgs.);
8. Declaration under 37 C.F.R. §1.132 (4 pgs.);
9. Check number 586657 in the amount of $755.00; and
10. Return Receipt Postcard.

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"EXPRESS MAIL" LABEL NUMBER **EM 023 788 864 US** DATE OF DEPOSIT **August 13, 2007**

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450 , ALEXANDRIA, VA 22313-1450.

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Check number 586657 in the total amount of $755.00 is enclosed as payment for the three-month Extension of Time fee ($225.00), Terminal Disclaimer fee ($65.00) and Information Disclosure Statement fee ($180.00). No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of this Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 13, 2007

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PATENT & TRADEMARK OFFICE

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

Responsive to the Office Action mailed February 12, 2007, please amend the above-identified application as follows:

Amendments to the Specification are reflected beginning on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 7 of this paper.

Remarks/Arguments begin on page 14 of this paper.

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Tim Lasher
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER)

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

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Amendments to the Specification

Please replace paragraph [0025] of the specification with the following amended paragraph:

[0025] In one aspect, the invention provides a method of controlling caloric intake by administering a composition having a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of INTRAVAIL® ~~Intravail~~ alkyl saccharide.

Please replace paragraph [0026] of the specification with the following amended paragraph:

[0026] In another aspect, the invention provides a method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of INTRAVAIL® ~~Intravail~~ alkyl saccharide.

Please replace paragraph [0030] of the specification with the following amended paragraph:

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25%TDM and IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following IP injection ~~oral~~ administration of glucose (i.e., in a so-called "glucose tolerance test").

Please replace paragraph [0045] of the specification with the following amended paragraph:

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a hydrophilic ~~hydrophobic~~ saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

Please replace paragraph [0051] of the specification with the following amended paragraph:

[0051] Accordingly, a subject treated with surfactant compositions of the invention having at least one alkyl glycoside, e.g. tetradecylmaltoside (TDM; or INTRAVAIL® ~~Intravail~~ A), at a concentration of about 0.125% by weight of alkyl glycoside two times per day, or three times per day, or more depending on the treatment regimen consumes about 200 to 300 micrograms per day total of TDM. So, the effective dose of the TDM is at least 1000X fold lower than (i.e., 1/1000) of the NOAEL, and falls far below 1% of the NOAEL, which is the acceptable daily intake; or in this case about 1/50,000 of the acceptable daily intake.. Stated another way, alkyl glycosides of the present invention have a high NOAEL, such that the amount or concentration of alkyl glycosides used in the present invention do not cause an adverse effect and can be safely consumed without any adverse effect.

Please replace paragraph [0117] of the specification with the following amended paragraph:

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other ~~highly branched~~ long alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Please replace paragraph [0135] with the following amended paragraph:

[0135] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase in the blood glucose levels as shown in FIG. 2 (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhibition of pancreatic insulin secretion. Blood glucose levels peak to about 482 mg/dl by 30 minutes after the xylazine-ketamine injection (FIG. 2). Then, at approximately 33 minutes after the xylazine-ketamine injection, 6 μL of insulin

~~(Humalog)~~ (HUMALOG®) in 0.25% tetradecylmaltoside (TDM; or INTRAVAIL® ~~Intravail~~ A) was administered intranasally using a long thin micropipette tip, and blood glucose levels were monitored at about 15 minute intervals. After administration of the 0.25% TDM/insulin composition, there was a rapid decrease in blood glucose levels, reaching a low of about 80 mg/dl at about the 60 minute time point, or about 30 minutes after the insulin administration (FIG. 2). At about the 75 minute time point, blood glucose levels gradually returned to the baseline level in a normoglycemic mouse, or about 80-100 mg/dl.

Please replace Table 1 at p.44 with the following amended table:

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	~~144~~ 141 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

Please replace the header of Example 5 at page 47, with the following amended title:

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS GLUCAGON ~~INSULIN~~ PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

Amendments to the Claims

Please amend claims 1, 4-6, 12, 14-18, 20-31, 33-38, 40-42, and 44-46 as provided below.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A surfactant composition comprising ~~of~~ at least one alkyl glycoside ~~and/~~or at least one saccharide alkyl ester~~, and when~~ admixed with a drug, wherein the surfactant maintains ~~stabilizes~~ the biological activity and increases the bioavailability, of the drug[[.]] ,

wherein the drug is selected from the group consisting of insulin, glucagon and exendin-4, and wherein the alkyl glycoside is selected from the group consisting of sucrose dodecanoate, dodecyl maltoside, and tridecyl maltoside.

2. (Withdrawn) The composition of claim 1, wherein the drug is a peptide or a protein.

3. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. (Currently Amended) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than ~~the~~ an acceptable daily intake amount of the surfactant.

5. (Currently Amended) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than ~~the~~ an acceptable daily intake amount of the surfactant.

6. (Currently Amended) The composition of claim 1, wherein ~~the~~ a surfactant has a high no observable adverse effect level at least 1000 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

7. (Original) The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. (Original) The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. (Original) The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. (Currently Amended) The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system of a subject.

13. (Original) The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. (Currently Amended) The composition of claim 1, wherein the surfactant is at a concentration ~~is from~~ of about 0.01% to 20% (w/v).

15. (Currently Amended) The composition of claim 1, wherein the surfactant ~~concentration~~ is at a concentration of ~~from~~ about 0.01% to 5% (w/v).

16. (Currently Amended) The composition of claim 1, wherein the surfactant is at a concentration of ~~is from~~ about 0.01% to 2% (w/v).

17. (Currently Amended) A therapeutic composition comprising ~~of~~ at least one biologically active compound(s) and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside ~~and/~~or saccharide alkyl ester and wherein said composition maintains ~~stabilizes~~ the biological activity of ~~the~~ a drug, for at least about 6 months from about 4°C to 25°C, wherein the drug is exendin-4.

18. (Currently Amended) The composition of claim 17, wherein ~~the pH of~~ the composition has a pH ~~is~~ less than 8.0.

19. (Original) The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. (Currently Amended) The composition of claim 17, wherein the composition has a concentration of ~~is from~~ about 0.01% to 20% (w/v).

21. (Currently Amended) The composition of claim 17, wherein the composition has a concentration of ~~is from~~ about 0.01% to 5% (w/v).

22. (Currently Amended) The composition of claim 17, wherein the composition has a concentration of ~~is from~~ about 0.01% to 2% (w/v).

23. (Currently Amended) [[A]] The ~~stable~~ therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. (Currently Amended) [[A]] The ~~stable~~ therapeutic composition according to claim 17, wherein ~~the~~ administration to a ~~the~~ subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of the ~~said~~ biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of the ~~said~~ subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the ~~said~~ subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to ~~the~~ a subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of the ~~said~~ biologically active compound(s) to the subject.

27. (Currently Amended) The therapeutic composition of claim 17, wherein said composition following mucosal administration to a ~~said~~ subject yields an area under concentration curve (AUC) of the ~~said~~ biologically active compound(s) in the ~~said~~ CNS tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of the ~~said~~ biologically active compound(s) in the ~~said~~ CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of the ~~said~~ biologically active compound(s) to the ~~said~~ subject.

28. (Currently Amended) The therapeutic composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields an area under concentration curve (AUC) of the ~~said~~ biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in the ~~said~~ CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. (Currently Amended) The therapeutic ~~pharmaceutical~~ composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. (Currently Amended) The ~~pharmaceutical~~ composition of claim 17, wherein the composition following mucosal administration to a ~~the~~ subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. (Currently Amended) A method of administering a drug composition comprising ~~of~~ a surfactant having at least one alkyl glycoside ~~and/~~or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the ~~stability and~~ bioavailability of the drug.

32. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

34. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

35. (Currently Amended) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than an acceptable ~~the~~ daily intake amount of the surfactant.

36. (Currently Amended) The method of claim 31, wherein the surfactant reduces variance in ~~the~~ bioavailability ~~variance~~ from patient to patient.

37. (Currently Amended) The method of claim 31, wherein the composition does not enter the hepatic portal blood system of a subject.

38. (Currently Amended) The method of claim 31, wherein ~~the pH of~~ the composition has a pH ~~is~~ less than 8.0.

39. (Original) The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. (Currently Amended) The method of claim 31, wherein the composition has a concentration of ~~is from~~ about 0.01% to 20% (w/v).

41. (Currently Amended) The method of claim 31, wherein the composition has a concentration of ~~is from~~ about 0.01% to 5% (w/v).

42. (Currently Amended) The method of claim 31, wherein the composition has a concentration of ~~is from~~ about 0.01% to 2% (w/v).

43. (Original) The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. (Currently Amended) The composition ~~method~~ of claim 1, wherein the composition ~~is~~ further comprises ~~comprised of~~ an enteric coating.

45. (Currently Amended) The composition ~~method~~ of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM) or dodecylmaltoside (DDM).

46. (Currently Amended) The method of claim 45, wherein the TDM or DDM has anti-bacterial activity.

47 to 138. (Cancelled).

REMARKS

The remarks are in response to the Office Action dated February 12, 2007. Claims 1, 4-6, 12, 14-18, 20-31, 33-38, 40-42, and 44-46 have been amended. Claims 47-138 were previously cancelled without prejudice. Subsequent to the entry of the present amendment, claims 1 and 3-46 will be pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

Information Disclosure Statement

The Office Action alleges that the manuscripts listed in paragraph [0141] fail to comply with the provisions of 37 C.F.R §§1.98(b) because the references were not submitted in a separate paper and may not be incorporated into the specification. Applicants respectfully submit that four of the articles cited by the Examiner, and provided below, were previously submitted in an information disclosure statement filed on October, 31 2005. Accordingly, Applicants respectfully request withdrawal of the Examiner's objection with regard to the references.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132:107-113.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides. B. Oral absorption *in vivo* in rats," *Int. J. Pharmaceutics* 132:115-121.

Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213.

The Office Action also alleges that two additional manuscripts included in paragraph [0141] fail to comply with the provisions of 37 C.F.R §§1.98(b) because the references were not submitted in a separate paper and may not be incorporated into the specification. Attached herewith is a submission of an IDS on a form PTO/SB/08 1449 for consideration by the Examiner. Applicants respectfully request withdrawal of the objection.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 17-46 are rejected under 35 U.S.C. §112, for allegedly failing to meet the written description requirement. Applicants respectfully traverse the rejection as it applies to the pending claims.

It is well-established that "[a] objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). *Under Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed". See MPEP §2163.04.

Applicants respectfully submit that support for claims 17-46 can be found in, for example, paragraph [0048] of the specification as filed. Further, in view of the art known at the time of filing, Applicants submit that the specification, as filed, conveys with reasonable clarity that the Applicants were in possession of the claimed invention as of the filing date.

For example, the present specification highlights U.S. Patent No. 5,726,154 (hereafter "the '154 patent"), which is incorporated by reference in its entirety, which describes characteristics of similar therapeutic compositions to those claimed in the present invention. The '154 patent describes aqueous mixtures of an effective amount of a surfactant (SDS) and an effective amount of organic acid in order to provide storage of calcitonin for up to 6 months at between 4°C - 25°C (see, e.g., Tables 1 and 2, columns 5 and 6 respectively of the '154 patent).

Applicants submit that the '154 patent establishes what was known in the art at the time the application was filed and that the present invention amply demonstrates the Applicants were in possession of the invention at the time of filing. (see for example, claim 13 and paragraph [0006] of the specification as filed). Applicants further submit that the bioavailability data presented in, for example, Figure 1 and paragraphs [0117] and [0118], allow the skilled artisan to extrapolate pharmacokinetic parameters such as, for example, C_{max} and AUC. Thus, Applicants respectfully submit that the specification clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date, the Applicants were in possession of the claimed invention.

Accordingly, withdrawal of rejection of claims 17-46 under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 31-46 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that those of ordinary skill in the art would be able to utilize the present specification to determine appropriate therapeutic compositions to administer to a subject in need thereof. (see for example, paragraphs [0040]-[0045], among others). Applicants further submit that the skilled artisan would sufficiently understand the terms "subject" and "biologically active" provided in the specification, as filed, and respectfully direct the Examiner's attention to paragraphs [0035] and [0036] of the specification wherein example therapeutic peptides are disclosed.

However, without acquiescing to the reasoning offered by the Office, and in order to advance prosecution of the instant application, Applicants have amended claims 1, 37, and 40-42 to provide greater particularity to terms "subject" and "biologically active" thus, the rejection no longer applies to the claims. Support for the amendments may be found in Examples 3, 4, 5, 6

and 7 and, for example, in paragraphs [0026], [0030] and [0070], among others of the specification as filed. Paragraph [0070] of the present specification, for example, describes a number of agents known in the art to be biologically active against specific pharmacological targets. As such, Applicants submit that the skilled artisan would sufficiently understand term "biologically active" as described in the specification as filed. Further, paragraph [0010] of the specification as filed, for example, provides a description pertaining to a "subject" as follows:

> The present invention also provides a method of treating diabetes including administering to a *subject* in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell), a blood glucose reducing amount of a therapeutic composition, for example, an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of incretin mimetic agent or insulin and lowering the level of blood glucose and treating diabetes in the *subject*. (paragraph [0010])

Thus, Applicants respectfully assert the skilled artisan would understand the term "subject" to encompass organisms with oral, ocular, nasal, etc., routes of administration and organisms subject to disease states such as, for example, diabetes. Applicants submit that the specification enables the skilled artisan to practice the claimed invention and respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. §112, second paragraph

Claims 2, 4-6, and 14-46 are rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection as it applies to the pending claims. Applicants respectfully submit that it appears that the Examiner's rejection of claim 24 in the Office Action dated February 12, 2007, should be directed to claim 36. Accordingly, the following comments pertain, in part, to rejection of claim 36.

Claims 20-22 and 40-42 are rejected as allegedly being confusing and indefinite because they claim a therapeutic composition and also refer to a composition concentration that is less than 100%.

Applicants have amended claims 14-16 to emphasize that the concentration of surfactant is 0.01% to 20%(w/v), 0.01% to 5%(w/v) and 0.01% to 2%(w/v) respectively. Applicants respectfully submit that the skilled artisan would be knowledgeable in utilizing the level of skill in the art, at the time of filing, to properly formulate the present invention and practice the present invention, see for instance, paragraph [0094] of the specification as filed. For example, the skilled formulation scientist would have been knowledgeable in assessing formulation parameters, such as, for example, solubility, hygroscopicity and other physicochemical characteristics of the claimed invention and thus, would be able to formulate it appropriately in light of the specification as filed. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Office Action also alleges that claims 3-6 and 32-35 contain the indefinite term "high". Applicants direct the Examiner's attention to paragraphs, for example, [0049], [0050] and [0051] wherein the term "high" is described with sufficient clarity to convey to the skilled artisan the meaning of the term as it pertains to NOAEL. Applicants therefore, submit that the skilled artisan would understand the term "high" as it pertains to (NOAEL). Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1-13, 17-19, 23-36, 38-39 and 43 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Hovgaard et al. (hereinafter, "Hovgaard"). Applicants respectfully traverse the rejection as it applies to the pending claims.

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference,

and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

Applicants respectfully submit that contrary to the Examiner's assertion Hovgaard does not teach each and every element of Applicant's claimed subject matter because the present invention claims an alkyl glycoside which possesses a significantly lower alkyl glycoside to drug ratio than that described by Hovgaard. Applicants direct the Examiner's attention to paragraph [0117] of the present specification which describes the differences in character (i.e., glycoside:drug ratio) between Hovgaard and the present invention. As a result, bioavailability attributable to the respective compositions are variable. (see paragraph [0117]). Thus, Hovgaard does not teach all the elements of the present invention and Applicants respectfully request that the rejection be withdrawn.

Claims 1-17 and 19-30 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Watanabe et al. (hereinafter, "Watanabe"). Applicants respectfully traverse the rejection as it applies to the pending claims. Applicants respectfully submit that Watanabe describes anti-bacterial agents which are applicable to *food additives* for the purposes of increasing shelf life, not to increasing absorption of a therapeutic agent in a subject. Further, many of the compositions described in Watanabe exhibit no antibacterial activity whatsoever. The reference also fails to show enhanced mucosal absorption in galactose and fructose laurates. Finally, Watanabe fails to teach compositions which maintain biological activity and increases bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-30 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Sekiguchi et al. (hereinafter, "Sekiguchi", U.S. Patent No. 5,109,127). Applicants respectfully traverse the rejection as it applies to the pending claims. Applicants respectfully submit that Sekiguchi does

not anticipate because it does not teach each and every element of the claimed invention. Specifically, Sekiguchi describes compositions which have "excellent foaming power" which can be achieved by controlling the content of mono, di, and tri-esters within specified ranges. (see column 1, line 45). Applicants respectfully submit that Sekiguchi describes compositions which improve hair and toothpaste quality, (see Examples 8, 9 and 10 of Sekiguchi), and do not enhance therapeutic drug absorption in a subject. Further, Sekiguchi fails to disclose compounds which are stable for at least 6 months in the claimed temperature ranges. In addition, Sekiguchi fails to demonstrate that the compositions described function other than to provide a foaming power with high safety in toothpaste or in preventing a "slimy feeling" when applied to hair. (see Column 17, line 3, for example, among others). Accordingly, since Sekiguchi does not disclose each and every element from the claimed invention, a finding of anticipation cannot be reasonably sustained. Applicants respectfully request that the rejection be withdrawn.

Claims 1-43 and 45-46 are rejected under §102(b) as allegedly anticipated by Kee et al. (hereinafter, "Kee", U.S Patent No. 5,369,095). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office Action alleges that Kee describes *topical* use of substituted glycosides for penetration of drugs across mucus covered epithelium. However, Kee fails to describe a method for enhanced absorption wherein the therapeutic agent is delivered *systemically* in a subject in need thereof. As described in the abstract, and claims 1-10, for example, Kee clearly relies on enhancing *topically* applied therapeutic agents and does not teach enhanced *systemic* exposure as in the presently claimed invention. Applicants' claimed method is distinguished from that of Kee since Applicant's invention is directed to a composition which increases bioavailability of a drug. Applicants submit that the method of Kee is limited to *topical* ophthalmic use with the objective of obtaining penetration of the drug into the eye *without* system exposure or absorption. For example, Kee discloses at lines 52-61 of column 2:

> The present invention is based on the discovery that substituted glycosides effectively and safely enhance the corneal penetration of ophthalmic drugs. When "corneal penetration" is used herein it includes penetration through the cornea, sclera, and conjunctiva of the eye. These penetration enhancers can be used in compositions comprising any ophthalmic drug which to be effective must be substantially taken up by the aqueous humor, ciliary processes and other tissues in the eye upon topical administration.

Lines 66-69 of column 4 and lines 1-9 of column 5 further provide:

> The use of substituted glycosides in accordance with the present invention to enhance corneal penetration of drugs significantly increases the amount of drug which is able to penetrate the cornea. The degree of enhancement will vary with different drugs, but in some cases may be as much as 3-fold or more. Because drugs can more effectively penetrate the cornea, less drug is lost due to flow down the punctum and therefore less drug need be administered to effectively treat a particular indication. This is particularly beneficial when it is necessary to administer drugs which cause severe systemic side effects.

Therefore, it is clear that the method of Kee is for topical application and penetration of drug into the eye without systemic absorption. Finally, Kee fails to disclose compounds which maintain biological activity and increase bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. Since Kee fails to disclose each and every element of the invention Applicants respectfully request withdrawal of the rejection as they apply to the pending claims.

Claims 1-10 and 12-13 are rejected under §102(b) as allegedly anticipated by Lamberti et al. (hereinafter, "Lamberti", U.S Patent No. 3,849,341). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Office Action alleges that Lamberti discloses ester-linked compounds including di-, oligo-, and polysaccharide alkyl glycosides described by formula I. Lamberti describes use of certain ester-linked carboxylate derivatives which can serve as "*effective detergent builders*". The Lamberti composition also describes compounds containing an alkali metal linked to

carboxylate and phenylene. (see Column 2, line 33). However, Lamberti does not disclose use of a therapeutic agent and therefore does not describe *each and every element* of the claimed invention. Further, the present invention does not disclose compounds containing either alkali metals nor which work as "detergent builders" in preventing eutrophication. Applicants respectfully submit that contrary to Lamberti, the present invention claims the use of certain alkyl glycosides for the purpose of enhancing therapeutic absorption. Further, Lamberti fails to disclose compounds which maintain biological activity and increase bioavailability for at least 6 months in the claimed temperature ranges. Since *each and every element* is not disclosed, Lamberti cannot anticipate the claimed invention. Thus, Applicants respectfully request withdrawal of the rejection.

Claims 1-7 and 9-14 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Koike et al. (hereinafter, "Koike" U.S. Patent No. 5,639,733). Applicants respectfully traverse the rejection as it applies to the pending claims. The Office Action alleges that Koike discloses alkyl glycoside aqueous solutions which have a pH exceeding 7, and/or contains a water soluble alcohol, wherein the solution is stable to microbial activities such as putrefaction and fungal growth. Applicants respectfully submit that Koike fails to disclose compounds that may be administered systemically. Koike also fails to teach administration of the claimed compositions to enhance administration of a therapeutic agent while also avoiding adverse toxic levels of a drug. Further, Koike fails to disclose compounds which maintain biological activity and increase bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. Since *each and every element* is not disclosed, Koike cannot anticipate the claimed invention. Applicant's respectfully request withdrawal of the rejection.

Claims 1-43 and 45-46 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meezan et al. (hereinafter, "Meezan '130" U.S. Patent No. 5,661,130). Applicants respectfully traverse the rejection as it applies to the pending claims. The Office Action alleges that Meezan

discloses preferred glycosides including maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12 or 14 carbon atoms. Applicants submit however, that Meezan '130 does not describe working examples which provide for a NOAEL as claimed in the present invention. Further, Meezan '130 does not provide working examples or disclose compounds which maintain biological activity and increase bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. Since *each and every element* is not disclosed, Meezan '130 cannot anticipate the claimed invention. Applicant's respectfully request withdrawal of the rejection.

Claims 1-13, 17-19, 23-27, 39, 43 and 45-46 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meezan et al. (hereinafter, "Meezan '634" U.S. Patent No. 5,817,634). Applicants respectfully traverse the rejection as it applies to the pending claims. The Office Action alleges that Meezan '634 describes methods of treating diabetes or glycogen storage disease by increasing cellular glucose. However, Meezan '634 does not disclose compositions which are useful in enhancing the systemic absorption of a therapeutic agent. Further, contrary to Meezan '634, the present invention claims compositions which can achieve a specified NOAEL in a subject. Finally, Meezan '634 does not disclose compounds which maintain biological activity and increase bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. Since *each and every element* is not disclosed, Meezan '634 cannot anticipate the claimed invention. Applicant's respectfully request withdrawal of the rejection.

Claims 1-13 and 45-46 are rejected under 35 U.S.C. §102(f) because the Examiner alleges that Applicants did not invent the claimed subject matter. Applicants respectfully traverse the rejection as it applies to the pending claims.

Without acquiescing to the Office's reasoning, claim 1 has been amended to recite a surfactant composition admixed *with* a drug, thus, the rejection no longer applies. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1-46 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Meezan et al. (U.S. Patent No. 5,661,130; hereinafter "Meezan '130") in view Crotts et al. (US 2003/0017203; hereinafter "Crotts"). Applicants respectfully traverse the rejection as it applies to the pending claims. Applicants submit that in cases of obviousness, the Supreme Court has held:

> when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and *common sense*. (*KSR v. Teleflex,* 550 U.S.Sup.Ct. May 2007)

Further, the burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984).

The Office Action alleges that Meezan '130 discloses calcitonin compositions comprising alkyl glycoside absorption enhancers. However, Meezan '130 does not teach or suggest that its compounds which maintain biological activity and increase bioavailability for at least 6 months in the temperature ranges of about 4°C to 25°C. It also does not disclose working examples of compositions which yield the NOAEL achievable in the present invention. The Office Action also alleges that Crotts cures the deficiencies of Meezan '130 because it describes compositions as absorption enhancers which may allegedly be comprised of any peptide that is useful in the treatment of a disease or condition. However, Crotts fails to teach or suggest compositions with the specified *in vivo* character of the present invention and also fails to describe compounds which exhibit the claimed stability. Crotts describes "stability results" for its compositions wherein:

> 15% of the drug could *not* be accounted for from the 0.5 mg tablet after six months of storage at ambient temperature. (see paragraph [0062], line 17)

It further goes on to state:

> These data suggest that the room temperature storage stability is probably between *three and six months*. (see paragraph [0062] line 23)

Accordingly, even when considered with improper hindsight the skilled artisan would not accept that the compositions disclosed in Meezan '130, along with the enteric coating of Crotts, would render the present invention obvious because Crotts inherently teaches away from the claimed subject matter. As discussed above, Crotts highlights that up to 15% of a drug was unaccounted for after six months of storage. Hence, there would be no foreseeable basis on which the skilled artisan would arrive at the stability and *in vivo* character of the present invention.

Therefore, Meezan '130 does not render the present invention obvious and Crotts does not cure its deficiencies. Accordingly, withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 are rejected under the judicially created doctrine of obviousness double patenting allegedly over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (hereafter "the '130 Patent"). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that the provisions of the Cooperative Research and Technology Enhancement Act (CREATE) of 2004 (Effective date September 14, 2005) apply in this case. Applicants respectfully submit that pursuant to an obligation to assign, Dr. Edward T. Maggio has currently assigned his rights in the present application to Aegis Therapeutics, LLC and Dr. Elias Meezan and Dr. Dennis J. Pillion have assigned the invention to the UAB Research

Foundation. As such, the provisions of CREATE apply in this instance because in this instance the invention does not share common ownership with U.S. Patent No. 5,661,130. According to 37 CFR, parts 1 and 3, Applicants must fulfill three basic requirements to invoke the provisions of the CREATE Act in this case. The requirements are summarized, in part, according to the following:

> The CREATE Act amends 35 U.S.C. 103(c) to provide that subject matter developed by another person shall be treated as owned by the same person or subject to an obligation of assignment to the same person for purposes of determining obviousness if three conditions are met: (1) The claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made; (2) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and (3) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement. *See* Pub. L. 108–453, 118 Stat. 3596 (2004). (See 35 U.S.C. §103(c)(2), 37 C.F.R., Parts 1 and 3).

Applicants respectfully submit that all three requirements have been met in the present case. Applicants submit herewith a declaration from Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio, attesting that the present invention was made as a result of activities undertaken within the scope of a joint research agreement. The declaration also discloses the names of the parties to the joint research agreement. Applicants respectfully submit that an amendment to the specification adding the names of the parties to the joint agreement, pursuant to the third requirement of the CREATE Act provisions, is not required, since the application as filed, discloses the requisite parties, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio.

Under the provisions of the CREATE Act, Applicants respectfully submit herewith a terminal disclaimer, disclaiming the terminal part of any patent granted on the above-identified Application, 11/127,786 that would extend beyond the expiration date of U.S. Pat. No. 5,661,130. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1, 8, 11, 31 and 43 are rejected under the judicially created doctrine of obviousness double patenting, allegedly over claims 1-6 and 12-13 of co-pending U.S. Application No. 11/193,825 (hereafter '825). Applicants respectfully traverse the rejection as it applies to the pending claims.

Applicants respectfully submit that claims 1, 17, 31 and 45 have been amended in order to add particularity in distinguishing the present invention from the '825 application, thus the rejection, as it pertains to these claims, no longer applies. Accordingly, Applicants assert that the Examiner has failed to meet his burden of demonstrating a *prima facia* case of obviousness and withdrawal of the rejection as they apply to the pending claims is respectfully requested.

Without acquiescing to the Office's reasoning, and in the interest of advancing prosecution in this case, Applicants submit herewith a terminal disclaimer. Thus, the rejection no longer applies to the pending claims and withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the total amount of $755.00 is enclosed as payment for the three-month Extension of Time fee ($510.00), Terminal Disclaimer fee ($65.00) and Information Disclosure Statement fee ($180.00). No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 13, 2007



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OIPE IAP66 AUG 13 2007 PATENT & TRADEMARK OFFICE

APPLICANTS: Meezan et al.
TITLE: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION
Application No.: 11/127,786 File Date: May 11, 2005
Docket No.: AEGIS1210

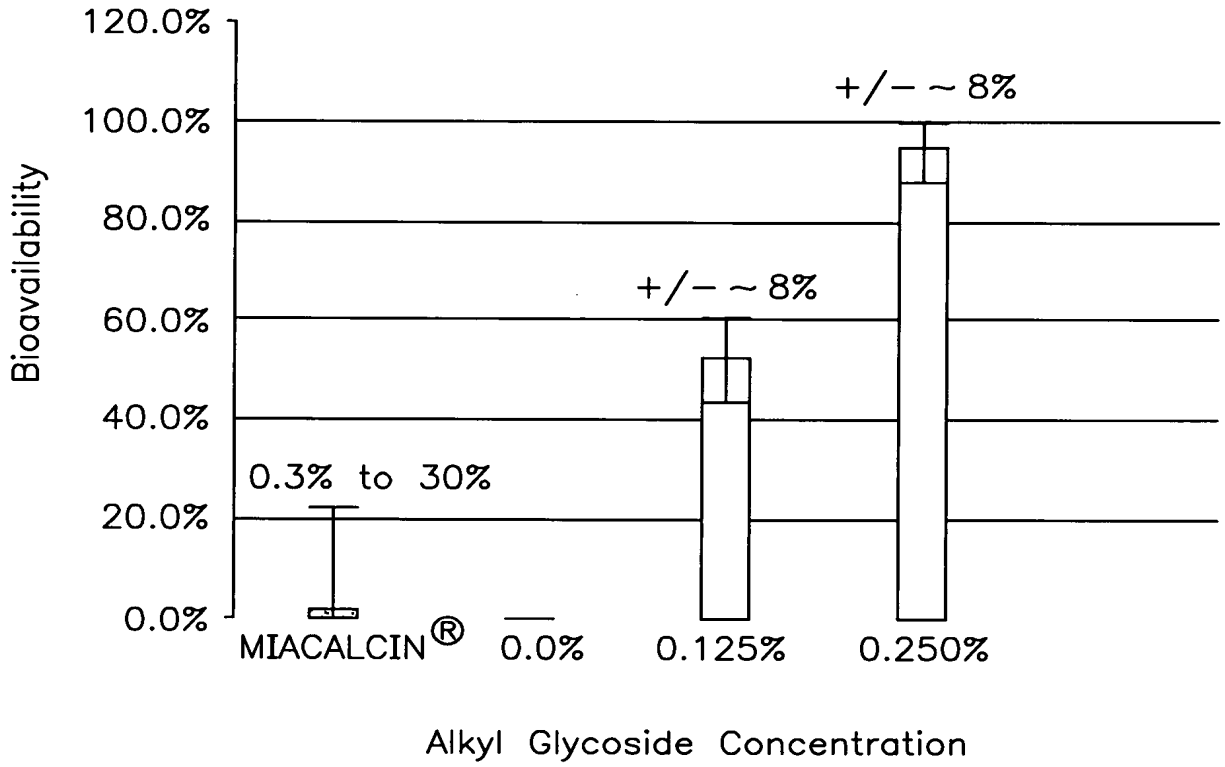


FIG. 1

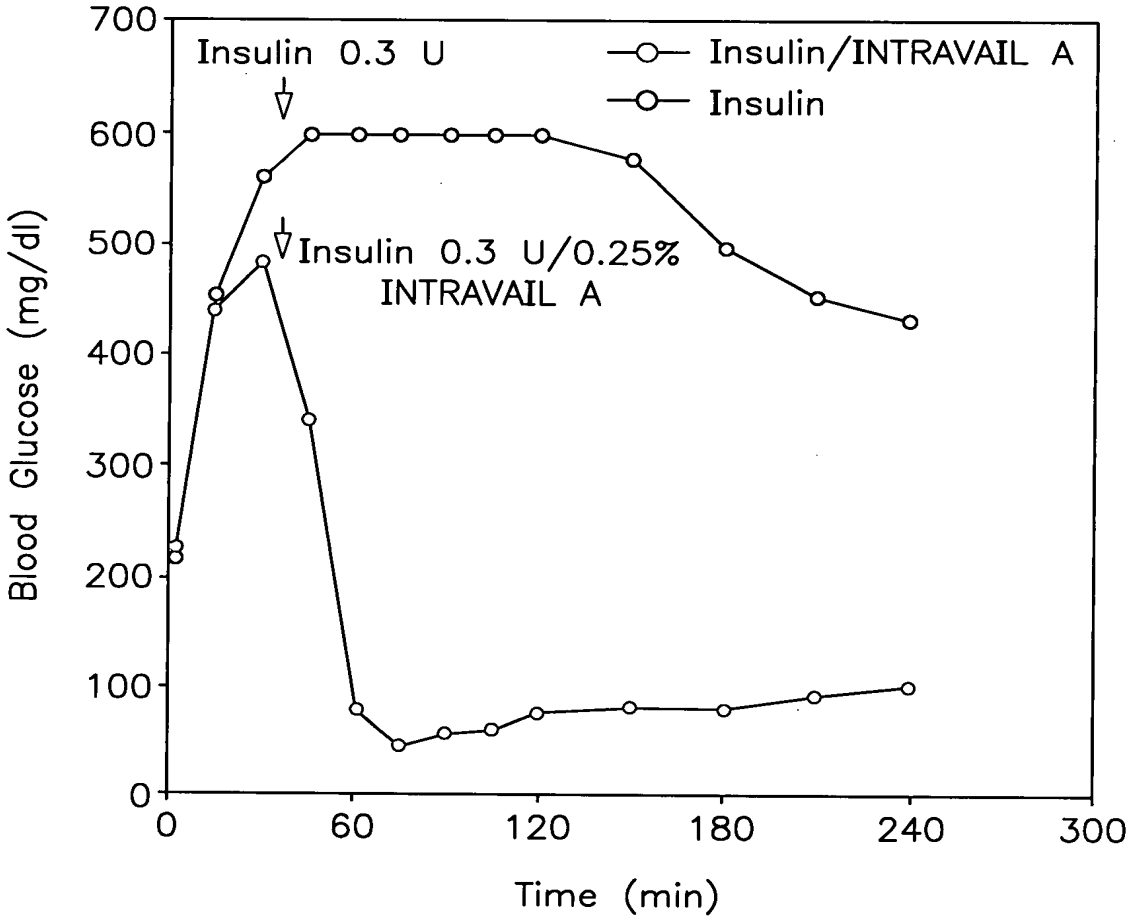

700
600
500
400
300
200
100
0
Blood Glucose (mg/dl)
Insulin 0.3 U
Insulin/INTRAVAIL A
Insulin
Insulin 0.3 U/0.25%
INTRAVAIL A
0
60
120
180
240
300
Time (min)

FIG. 2

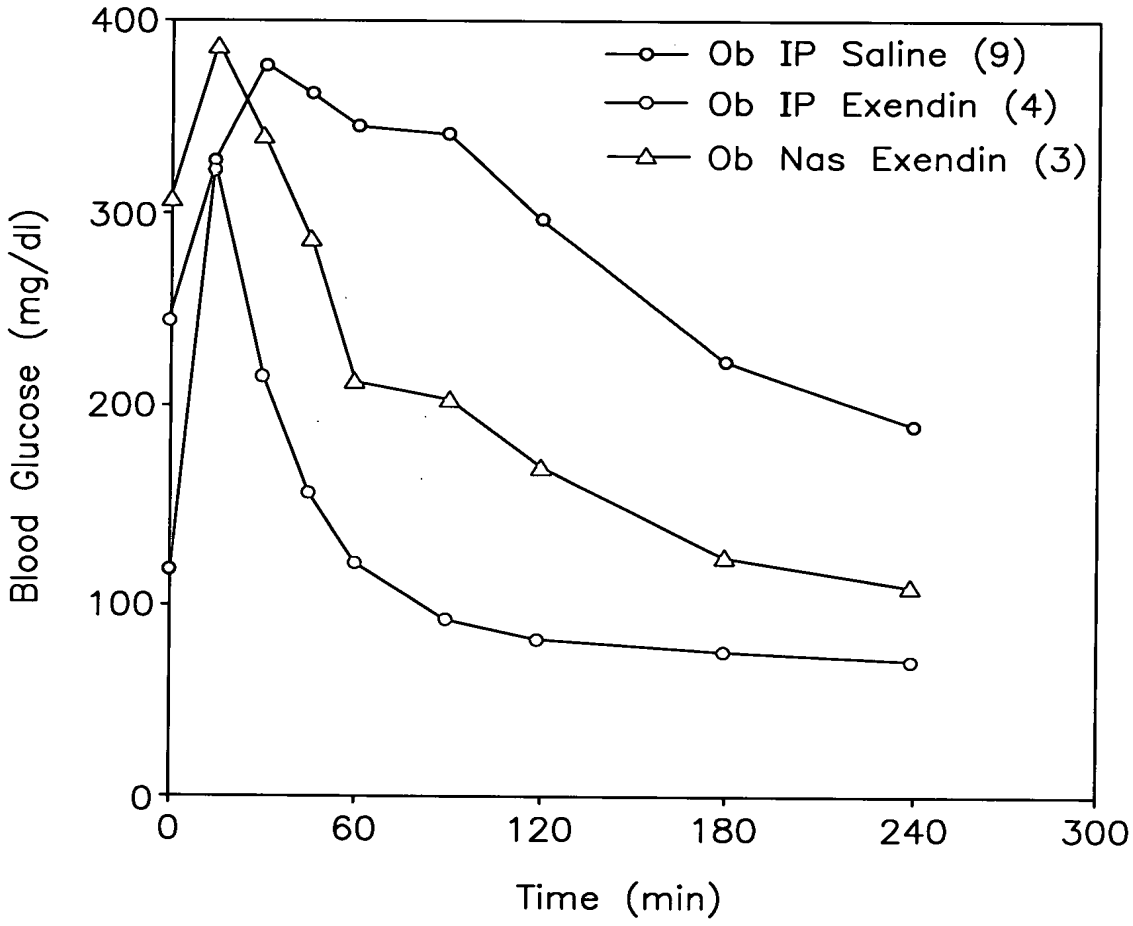

400
300
200
100
0
Blood Glucose (mg/dl)
0
60
120
180
240
300
Time (min)
Ob IP Saline (9)
Ob IP Exendin (4)
Ob Nas Exendin (3)

FIG. 3



PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

We, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio declare and state that:

1. We are co-inventors of the subject matter described and claimed in the U.S. Patent Application Serial No. 11/127,786, filed on May 11, 2005, entitled, "ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION", which claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now abandoned; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now abandoned; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now abandoned.

2. We are familiar with the prosecution history of U.S. Patent Application Serial No. 11/127,786.

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3. We understand that the Examiner rejected claims 1-8, 14-17, 20-23, 31, 40-42, 43 and 45-46 under the judicially created doctrine of obviousness double patenting allegedly over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130.

4. We attest that the present invention does not share common ownership with U.S. Patent No. 5,661,130 and that Dr. Edward T. Maggio has currently assigned his rights in the present application to Aegis Therapeutics, LLC and Dr. Elias Meezan and Dr. Dennis J. Pillion have assigned their rights in the present application to the UAB Research Foundation.

5. We attest that the subject matter of U.S. Patent Application Serial No. 11/127,786 complies with the provisions of the Cooperative Research and Technology Enhancement Act (CREATE) of 2004, 35 U.S.C. §103(c)(2), 37 C.F.R. Parts 1 and 3 (Effective date September 14, 2005) and further attest that all requirements of the Act, as they may pertain to the present case, are hereby met.

6. We attest that the present invention was made as a result of activities undertaken within the scope of a joint research agreement and further declare, that the application as filed, discloses the proper names of the parties to the joint research agreement.

7. We attest that an amendment to the specification adding the names of the parties to the joint agreement, pursuant to the CREATE Act provisions, is not required, since the application as filed, discloses the requisite parties, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio.

8. We declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date

Dr. Elias Meezan

Date

Dr. Dennis J. Pillion

Aug 13, 2007

Date

Dr. Edward Maggio

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PATENT
Atty Docket No.: AEGIS1210

Application of:
Meezan et al.
ication No.: 11/127,786
: May 11, 2005
3

8. We declare that all statements made herein of my own knowledge are true and
: all statements made on information and belief are believed to be true, and further that these
tements were made with the knowledge that willful false statements and the like so made are
nishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code,
d that such willful false statements may jeopardize the validity of the application or any patent
suing thereon.

8/13/07
Date

Dr. Elias Meezan

Date

Dr. Dennis J. Pillion

Date

Dr. Edward Maggio

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AUG 13 2007
PATENT & TRADEMARK OFFICE

PATENT
Atty. Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1616
Application No.:	11/127,786	Examiner:	J.H. Alstrum Acevedo
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER UNDER CREATE ACT OF 2004

Sir:

The undersigned, attorney of record for Petitioners, Aegis Therapeutics, L.L.C. and the UAB Research Foundation, represents that Petitioners are the Assignee of 100 percent interest in Application Serial No. 11/127,786, filed May 11, 2005, entitled ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION as evidenced by the Assignment recorded in the United States Patent and Trademark Office on May 23, 2005, at Reel 016052, Frame 0555 (Aegis Therapeutics L.L.C.) and on August 2, 2005, at Reel 016343, Frame 0736. (The UAB Research Foundation). The evidentiary documents referred to herein have been reviewed by the undersigned and it is certified that to the best of the undersigned's knowledge and belief, title is in the Assignee.

Petitioners respectfully submit that the subject matter of U.S. Patent Application Serial No. 11/127,786 complies with the provisions of the Cooperative Research and Technology Enhancement Act (CREATE) of 2004, 35 U.S.C. §103(c)(2), 37 C.F.R., Parts 1 and 3, (Effective

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"EXPRESS MAIL" LABEL NUMBER **EM 023 788 864 US** DATE OF DEPOSIT **August 13, 2007**

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Tim Lasher
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER)

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

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date September 14, 2005) with respect to U.S. Patent 5,661,130. Petitioners hereby invoke the provisions of the CREATE Act as they apply to the present application for submission of this Terminal Disclaimer.

Petitioners respectfully submit that, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio are co-inventors of the subject matter described and claimed in the U.S. Patent Application Serial No. 11/127,786, filed on May 11, 2005, entitled, "ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION", which claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now abandoned; the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now abandoned; the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now abandoned; the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now abandoned; and the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now abandoned.

Petitioners respectfully submit that the present invention does not share common ownership with U.S. Patent No. 5,661,130 and that Dr. Edward T. Maggio has currently assigned his rights in the present application to Aegis Therapeutics, LLC and Dr. Elias Meezan and Dr. Dennis J. Pillion have assigned their rights in the present application to the UAB Research Foundation. Petitioners further submit that the present invention was made as a result of activities undertaken within the scope of a joint research agreement and that the application as filed, discloses the proper names of the parties to the joint research agreement. Petitioners respectfully submit that an amendment to the specification adding the names of the parties to the joint agreement, pursuant to the CREATE Act provisions, is not required, since the application as filed, discloses the requisite parties, Dr. Elias Meezan, Dr. Dennis J. Pillion, and Dr. Edward Maggio.

Pursuant to 37 C.F.R. § 1.321(c) and the provisions of the CREATE Act, 35 U.S.C. §103(c)(2), 37 C.F.R., Parts 1 and 3, the undersigned, on behalf of Petitioners, Aegis Therapeutics, L.L.C. and the UAB Research Foundation, disclaim the terminal part of any patent granted on the subject matter of the above-identified U.S. Patent Application Serial No. 11/127,786, filed May 11, 2005, that would extend beyond the expiration date of U.S. Patent No. 5,661,130. Petitioner hereby agrees that any patent so granted on the above-identified U.S. Patent Application Serial No. 11/127,786 shall be enforceable only for and during such period that the patent shall be licensed to the same entity as granted U.S. Patent No. 5,661,130, this Agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successor or assigns.

A check in the amount of $755.00 is enclosed as payment for the three-month Extension of Time fee ($510.00), Terminal Disclaimer fee ($65.00) and Information Disclosure Statement fee ($180.00). No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 13, 2007

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PTO/SB/22 (12-04)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
Under the paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless if displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) AEGIS1210
Application Number 11/127,786	Filed May 11, 2005
For ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION	
Art Unit 1616	Examiner J.H. ALSTRUM ACEVEDO

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☐	Two months (37 CFR 1.17(a)(2))	$450	$225	$
☒	Three months (37 CFR 1.17(a)(3))	$1020	$510	$ 510.00
☐	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
☐	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

☒ Applicant claims small entity status. See 37 CFR 1.27.

☒ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 07-1896. I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

08/15/2007 EHAILE1 00000056 11127786
03 FC:2253 510.00 OP

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 38,347

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____.

Lisa Haile
Signature

August 13, 2007
Date

LISA A. HAILE, J.D., Ph.D.
Typed or printed name

(858) 677-1456
Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/127,786	05/11/2005	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/13/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 46	Minus	** 46	= 0	X $25 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $100 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
Juliet McMillan

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/127,786	05/11/2005	Elias Meezan	AEGIS1210	5393

28213 7590 02/12/2007

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	11/127,786	MEEZAN ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☒ Claim(s) *1 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2/05; 7/25/06; 9/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-46 are pending.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. It is noted that Applicants' have cited on form PTO-892 4 of the 6 references listed in paragraph [0141].

Drawings

The drawings are objected to because the trademarks MIACALCIN® (Figure 1) and INTRAVAIL® (Figure 2) should be written with all capital letters. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement-drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement

sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims 1 and 17 are objected to because of the following informalities: the word sequence "comprising of at" is grammatically incorrect (claims 1 and 17, line 1). Appropriate correction is required.

The use of the trademarks INTRAVAIL® ([0037], [0038], [0067], [0167], Example 7) and HUMALOG® ([0167] have been noted in this application. Trademarks should be capitalized wherever these appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' specification does not describe any of the following therapeutic compositions characterized by the stability of the biologically active compound being stabilized for at least 6 months from about 4 °C-25 °C in sufficient detail to demonstrate possession at the time the instant application was filed: (1) a composition comprising (a) at least one biologically active compound, (b) at least one alkyl glycoside, and (c) at least one saccharide ester; (2) (a) at least one biologically active compound and (b) at least one saccharide ester; nor (3) (a) at least one biologically active compound and (b) at least one alkyl glycoside. The specification is bereft of any data for therapeutic compositions (1)-(3) demonstrating that these had the claimed stability. It is noted that the definitions of alkyl glycoside and alkyl saccharide ester are extremely broad and include glycosides and saccharide esters that are oligomeric and polymeric.

Applicants' specification lacks data or written support to demonstrate that Applicants' were in possession of stable therapeutic compositions (1)-(3) wherein administration of said compositions to any subject is characterized by (a) peak concentration values (C_{max}) in CNS tissue/fluid or blood plasma of any biological active compound in any subject is about 15% or more greater than the C_{max} in CNS tissue/fluid

or blood plasma compared to intramuscular injection; (b) an area under curve (AUC) of the biologically active compound(s) in the CNS tissue/fluid or blood plasma of said subject that is 20% or greater compared to the AUC in the same subject's CNS tissue/fluid or blood plasma after intramuscular administration; and (c) a time to maximal concentration (t_{max}) of the biologically active agent in a CNS tissue/fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours. There is no AUC, t_{max}, or C_{max} data present in the instant specification or figures.

Claims 31-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering a drug composition comprising insulin, glucagon, or exendin-4 in combination with an alkyl glycoside selected from the group consisting of dodecyl sucrose, dodecyl maltoside, and tridecyl maltoside via ocular, nasal, intranasal, or intraperitoneal administration, does not reasonably provide enablement for the administration of compositions comprising any other biologically active agent in combination with any other alkyl glycoside or any alkyl saccharide ester. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513

(Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad. Applicants' are claiming a method of administering via any route of administration to any subject a composition comprising any drug, any alkyl glycoside, and/or any saccharide alkyl ester, wherein alky has from about 10-24 carbon atoms. The term subject is not defined in the specification. A reasonable broad interpretation of the word "subject" includes any living organism to which biologically active agents could be administered, such as amoeba, bacteria, fungi, trees, grasses, shrubs, humans, mammals, reptiles, fish, birds, invertebrates, and vertebrates. The term drug is defined in [0055] to include any molecule or therapeutic agent or therapeutic compound or biologically active compound. The term biologically active is not defined, therefore any molecule or compound that could have an effect on a biological system is biologically active, such as cyanide, elemental iron, elemental mercury, methyl mercury, DNA, RNA, antibiotics, proteins, enzymes, any organic molecule (e.g. salicylic acid, phosgene, chloromethyl methyl ether, etc.) water, etc. The terms alkyl glycoside and

saccharide alkyl ester are extremely broad, with only the limitation on the length of the alkyl groups somewhat limiting the scope. It is noted that there is no limitation on the number of alkyl groups a given alky glycoside or saccharide alkyl ester could have.

Nature of the invention/State of the Prior Art

The invention claims methods of administering to a subject a drug composition comprising a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alky has from about 10-24 carbon atoms and the surfactant increases the stability and bioavailability of the drug.

Routes of administration are known in the art, such as oral, buccal, nasal, rectal, vaginal, ocular, urethral, intrathecal, inhalation, injection (intramuscular, intravenous, intraperitoneal), etc. These various routes of administration often require that administered compositions have specific requirements. For example, inhalation administration requires that the inhaled compositions are characterized as aerosols (particulate solids or liquids suspended in an air or gas stream) having particle sizes below 10 microns (see Fig. 1 in Radhakrishnan et al. (U.S. Patent No. 5,192,528)) as well as other desirable aerodynamic properties (e.g. a density below 0.4 g/cm^3; See Edwards, USPN 6,254,854; e.g. col. 2, lines 1-60). Compositions intended for nasal or parenteral administration should be isotonic with the tissues through which or into which administration occurs and have a compatible pH (e.g. a pH between 4-7; see, for example, US 2003/0158206; or USPN 6,482,834; e.g. col. 36, line 1 through col. 37, line 6). The prior art also recognizes that administration of drugs resulting in the absorption

of drugs into CNS tissue/fluids is difficult (Beam et al. "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antibiotics in Rabbits with Intact and Inflamed Meninges," *Antimicrobial Agents and Chemotherapy*, **1977 (Dec.)**, *12(6)*, pp 710-716). Not all drugs are capable of crossing the blood brain barrier in detectable concentrations that would indicate absorption/bioavailability of these drugs in CNS tissue/fluids (pg. 712, right column, 2nd paragraph). Furthermore, a subjects' overall health could affect the ability of drugs to be absorbed by CNS tissues/fluids. For example, it was observed that in rabbits afflicted with pneumoccocal meningitis that tobramycin, an antibiotic, was measurable in cerebrospinal fluid (CSF), but not in brain tissue (abstract; pg. 710).

The prior art recognizes that ***some*** alkyl glycosides are characterized by the ability to enhance penetration (i.e. absorption) of drugs across mucosal epithelia and thereby the bioavailability of said drugs (e.g. Kee et al. USPN 5,369,095; IDS reference, Example 10, col. 11, lines 13-31 and Example 8, col. 10, lines 28-64). The alkyl glycosides that have this capability have alkyl groups ranging in length from 8 to about 14 carbon atoms and are comprised of monosaccharides (e.g. glucose or inositol) and disaccharides (i.e. maltose and sucrose). The prior art does not teach that polymeric or oligomeric alkyl glycosides (e.g. alkyl glycosides wherein the saccharide component is starch, cellulose, or chitin, for example) exhibit this same property. The prior art does not teach that saccharide alkyl esters have the property of enhancing absorption/penetration of drugs across mucosal epithelia.

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants' provide data demonstrating the ability of formulations comprising one alkyl glycoside selected from tetradecylmaltoside (TDM), dodecyl sucrose (DDS), dodecyl maltoside (DDM), and tridecyl maltoside (TriDM) promote absorption of drugs when administered intranasally (TDM only), ocularly (i.e. as eye drops), or interperitoneally (TDM only) enhance the absorption of drugs (i.e. insulin, glucagon, and exenedin-4) and as a result increase the bioavailabilty of said drugs. Applicants' have not provided any data demonstrating that compositions comprising a saccharide alkyl ester and a drug also exhibit similar increases in absorption and bioavailability. Applicants' data is only limited to blood plasma data. Applicants' data is not related to AUC, t_{max}, or C_{max}. Applicants' have not demonstrated evidence that the property of increased absorption/bioavailability attributed to the presence of any of the alky glycosides discussed above (i.e. TDM, DDS, DDM, and TriDM) can be extrapolated to absorption and bioavailability in CNS fluids/tissue.

In summary, the Examiner concludes that Applicants are only enabled for methods of administering a drug composition comprising insulin, glucagon, or exendin-4 in combination with an alkyl glycoside selected from the group consisting of dodecyl

sucrose, dodecyl maltoside, and tridecyl maltoside via ocular, nasal, intranasal, or intraperitoneal administration. Applicants' have not provided sufficient data and description to enable a person of ordinary skill in the art to administer compositions comprising any other biologically active agent in combination with any other alkyl glycoside (e.g. polymeric or oligomeric alkyl glycosides) or any alkyl saccharide ester. This lack of enablement would force the ordinary skilled artisan to undertake an burdensome quantity of experimentation to discover (1) which other alkyl glycosides (e.g. oligomeric and polymeric alkyl glycosides) to use; (2) which saccharide alkyl esters are suitable; and (3) how to formulate these compositions to enable absorption/bioavailability in CNS tissue/fluid as well as administer said compositions via other routes (e.g. orally or by inhalation).

To emphasize this point the Examiner directs Applicants to "Genentech, 108 F.3d at 1366 and *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)" which states,

> "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 4-6, and 14-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-6 recite the limitation "the daily intake amount" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 14-16 recite the limitation "the surfactant concentration" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "the drug" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claims 18 and 38 recite the limitation "the pH" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 21-22 and 40-42 recite the limitation "the composition concentration" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "the administration" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 25-30 recite the limitation "the subject" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "the bioavailability variance" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 12 and 37 recite the limitation "the hepatic portal blood system" in lines 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 is vague and indefinite because it is unclear what are the components of the drug composition utilized in the claimed method, because there appears to be one or more words missing after the word "comprising" on line 1 of said claim.

Claims 14-16 are confusing and indefinite because said claims claim a surfactant composition and also refer to a surfactant concentration from about 0.01% to 20%. However, the only required component of the claimed composition is a single surfactant. It is unclear what other components are present such that the surfactant is present in a concentration below 100%.

Claims 20-22 and 40-42 are confusing and indefinite because said claims claim a therapeutic composition and also refer to a composition concentration that is less than 100%. It is impossible for a composition to have a composition concentration less than unity, because if it is less than unity than what constitutes the claimed composition has not been described and an ordinary skilled artisan would not be apprised of the metes and bounds of the composition.

Claims 44-45 are vague and indefinite because these claims claim a method, however, these claims depends from claim 1, which claims a surfactant composition.

The term "high" in claims 3-6 and 32-35 is a relative term, which renders the claim indefinite. The term "high no observable adverse effect level" (i.e. high "NOAEL") is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted that the cited claims state that the claim states that the "NOEL" is a certain factor higher than the daily intake amount of the surfactant; however, the claim does not state what is the daily intake amount for any surfactant. Therefore, an ordinary skilled artisan would not be apprised of the metes and bounds of what constitutes a high NOEAL.

Claims 14-16, 20-22, and 40-42 are vague and indefinite because there are no units of measurement for the claimed concentrations; and therefore, it is unclear what is the concentration of the compositions required in the cited claims (i.e. are the amounts meant to be w/w, w/v, molarity, etc.).

Claim 12 is vague and indefinite, because the claimed composition does not comprise a drug, so it is unclear how the composition could have the property that the surfactant and the drug do not enter the hepatic portal blood system.

The remaining claims are rejected for depending from a rejected claim.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13, 17-19, 23-36, 38-39, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Hovgaard et al. (International Journal of Pharmaceutics, 1996, 132, pp 115-121; IDS reference).

Applicants' claim (1) a surfactant composition comprising at least one alkyl glycoside and/or at least one saccharide alkyl ester; (2) a therapeutic composition comprising at least biologically active compound(s) and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or saccharide alkyl ester, wherein said composition stabilizes the biological activity of the drug for at least 6 months from about 4°C to about 25°C; and (3) a method of administering a drug composition, wherein the drug composition a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10-24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

Note: The intended use of composition claims was given little weight in the determination of prior art (e.g. mixing with a drug or administration to a subject). It is noted that claims 1-13 read on a single surfactant compound.

Hovgaard discloses several surfactants in section 2.2 on page 117: **octylmaltoside (OM), decylmaltoside (DM), dodecylmaltoside (DDM), tetradecylmaltoside (TDM), hexadecylmaltoside (HDM), and octadecylmaltoside (ODM)**. These compounds read on claims 1-13, because these are all alkyl glycosides. Claim 8 reads on OM, DM, DDM, TDM, HDM, and ODM, which were disclosed by Hovgaard. The properties claimed in claims 3-7 and 13 are inherent to the disclosed compounds. A compound and its properties cannot be separated.

In section 2.3, left column, on page 117, Hovgaard discloses aqueous solutions comprising **insulin** (dosages of 25 U/ml/kg or 50 U/ml/kg), **DDM**, PBS buffer, water, wherein the solutions have a **pH of 7.4** and the weight ratios of insulin to DDM varied from 1:64 to 1:11. These solutions **were administered intraduodenally** (ID). The duodenum is comprised of mucosal tissue; therefore ID administration is a kind of mucosal administration. Insulin is a bioactive material (i.e. a protein drug).

Claims 1-17 and 19-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Watanabe et al. (*Current Microbiology*, 2000, *41*, pp 210-213; IDS reference).

Applicants' claims have been described above.

Watanabe discloses 21 different carbohydrate esters in Table 1 on page 211, including **galactose laurate and fructose laurate**. All the carbohydrate esters listed in Table 1 are characterized as having some antibacterial activity. All of these carbohydrate esters are inherently drugs, per Applicants' definition in paragraph [0050] that a drug is any biologically active compound. Drugs are therapeutic agents; therefore compositions having a drug are therapeutic compositions. Therapeutic compositions comprising 5 ml of brain heart infusion broth containing one of the carbohydrate esters listed on page 211 are disclosed on pg. 210, right column. In Table 3, Watanabe discloses a composition comprising 200 micrograms/ml of fructose laurate. The concentration of fructose laurate is equivalent to 0.02% w/v and therefore reads on claims 14-16 and 21-23.

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the

same composition, these must have the same properties, because a compound or composition and its properties may not be separated. It is also noted that Applicants' definitions do not prohibit the surfactants from also being therapeutic agents. As a result, the fructose laurate composition disclosed in Table 3 reads on therapeutic compositions comprising at least one biologically active compound and at least one saccharide alkyl ester.

Claims 1-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Sekiguchi et al. (U.S. Patent No. 5,109,127; "Sekiguchi").

Applicants' claims have been described above.

Sekiguchi discloses non-ionic surface-active agents (i.e. surfactants) comprising a **fatty acid ester of a hexose sugar (i.e. saccharide alkyl ester) or an alkyl glycoside** thereof (title; abstract; col. 3, line 31 through col. 4, line 2; claims 1-5). In column 24, lines 18-22, a surfactant composition comprising glucose monooctanoate, glucose dioctanoate, glucose monodecanoate, and glucose didecanoate.

Sekiguchi discloses several exemplified compositions such as a toothpaste composition in Example 8 (col. 24, lines 43-55) wherein the composition includes **1.0 % w/w glucose-6-monolaurate, 0.76% w/w sodium monofluorophosphate** (i.e. a therapeutic agent). Example 2 (col. 23, lines 50-57) discloses a kitchen detergent includes **10% w/w glucose octanoate** and **appropriate amounts of perfume and dye**. Suitable perfumes and appropriate amounts thereof are disclosed in column 22, lines 45-69 and column 23, lines 1-35, and include **1-menthol** (0.5 parts by weight; col. 23, line 21) and **citronella** (col. 22, line 59), which are both bioactive compounds. Example 23 (col. 27, lines 15-25) discloses a mouthwash composition, which includes **0.1% w/w**

citric acid (i.e. a bioactive compound involved in the physiologic oxidation of fats, proteins, and carbohydrates via the Krebs cycle), **0.4% w/w sodium citrate**, **2.0 % w/w glucose-6-monocaprylate, and 1.0 % w/w flavor**. Shampoo compositions having a pH of 5.8 are disclosed in Example 32 (col. 31, lines 6-42), wherein these compositions include a **C_{6-10} glucose ester (1-8% w/w) or C_{12} arabinose ester (5% w/w) and citric acid** in amount sufficient to obtain a **pH of 5.8**. Sekiguchi discloses that the surfactant can generally be blended into the compositions in amounts from **3-40% w/w** (col. 7, lines 44-46).

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the same composition, these must have the same properties, because a compound or composition and its properties may not be separated

Claims 1-43 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Kee et al. (U.S. Patent No. 5,369,095; IDS Reference; "Kee").

Applicants' claims have been described above.

Kee discloses **the use of substituted glycosides to enhance the penetration of drugs across mucus covered epithelial tissues of humans and animals**, including enhanced topically applied ophthalmic drugs through the corneal epithelium of humans and animals (title; abstract; claims 1-10). Mucus covered epithelial tissues of humans and animals include **nasal**, **pulmonary**, rectal, **buccal**, vaginal, uteral, and gastrointestinal tissues (col. 1, lines 19-23). Suitable ophthalmic drugs with which the alkyl glycosides can be used include **steroids, growth factors, cycloplegics, miotics,**

mydriatics, therapeutic proteins and peptides, antioxidants, aldose reductase inhibitors, nonsteroidal antiinflammatories, immunomodulators, antiallergics, antimicrobials, angiostatic agents and anti-glaucoma therapeutic agents (col. 2, lines 60-68).

The alkyl glycosides used in the Kee's invention have the following structure: R_1--Z--$(R_2)_x$, wherein R_1 is a hydrophobic group including saturated and unsaturated aliphatic hydrocarbon groups which range from 8 to 28 carbons in length with 1 to 5 double bonds. The aliphatic hydrocarbon group can be a straight or branched chain and may be substituted by one or more aromatic, cycloaliphatic or hydrophilic (e.g. hydroxyl, thiol, ester or amino) groups. R.sub.2 is a group derived from any cyclic or acyclic saccharide containing 4-7 carbons and their isomers; X is an integer from 1-10; and Z is an oxy (--O--), carbonyloxy, phosphoryl, thio (--S--), or carboxamido, where R_2 is covalently bound to such group (col. 3, lines 1-38). The most preferred penetration enhancer is **dodecyl maltoside** (col. 4, lines 41-50). Kee's invented glycosides include **tetradecyl maltoside (i.e. INTRAVAIL®), decyl maltoside, nonyl-beta-D-glucoside, sucrose monolaurate**, etc. (see, for example, col. 11, lines 20-31). Typically, one or more enhancers will be used in an amount of from about **0.01% to about 20% w/v, preferably from about 0.01-1.0% w/v** (col. 5, lines 20-23). In Example 1 (col. 6, line 28 through col. 7, line 15), Kee discloses the preparation of a pharmaceutical composition comprising an aqueous solution including *para*-amino-clonidine (i.e. a small molecule organic), dodecyl maltoside, benzalkonium chloride, etc.; and the ophthalmic administration (i.e. ocular administration) of an aliquot of 30 microliters (i.e. 0.03 mL) of the pharmaceutical aqueous solution formulation to New Zealand albino rabbits. In

Example 8 (col. 10, lines 28-64) Kee discloses the administration of a pharmaceutical aqueous solution comprising **dodecyl maltoside, reduced glutathione (a bioactive compound), atenolol (a bioactive compound)**, etc. The procedure of Example 8 was repeated multiple times in Example 10 (col. 11, lines 13-31) using different alkyl glycosides, including **tetradecyl maltoside**.

Claims 1-10 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamberti (U.S. Patent No. 3,849,341).

Applicants' claims have been described above.

Lamberti discloses ester-linked compounds including di-, oligo-, and poly-saccharide alkyl glycosides described by formula I (abstract; col. 2, lines 10-52), wherein the glycoside alkyl group R' is an alkyl group containing 1-4 carbon atoms or an alpha- or beta-fructose moiety having the structure depicted in col. 2, lines 39-45.

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the same composition, these must have the same properties, because a compound or composition and its properties may not be separated

Claims 1-7 and 9-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Koike (U.S. Patent No. 5,639,733).

Applicants' claims have been described above.

Koike discloses **alkyl glycoside aqueous solutions**, which have a **pH exceeding 7**, and/or contains a water-soluble alcohol, wherein the solution is stable to microbial

activities, such as putrefaction and fungal growth (title, abstract). Suitable alkyl glycosides are represented by formula (I) (col. 2, lines 30-48), wherein R' may be an **alkyl group** may be a straight or branched chain having **8-22 carbon atoms** and G is a reducing sugar having 5-6 carbon atoms. Examples of sugars used in the preparation of the alkyl glucosides include **monosaccharides** (e.g. glucose, galactose, ribose, etc.), **oligosaccharides** (e.g. lactose, sucrose, maltose, maltotriose), and **polysaccharides** (e.g. starch, dextrin, dextran, etc.).

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the same composition, these must have the same properties, because a compound or composition and its properties may not be separated

Claims 1-43 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130").

Applicants' claims have been described above.

Meezan discloses in claims 1-5 and 8-10:

1. A method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. **2.** The method of claim **1**, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%. **3.** The method of claim **1**, wherein the alkyl has from 9 to 24 carbons. **4.** The method of claim **3**, wherein the alkyl has from 9 to 14 carbon atoms. **5.** The method of claim **4**, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.	**8.** The method of claim **1**, wherein the compound is a protein or a peptide. **9.** The method of claim **8**, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon. **10.** The method of claim **8**, and further comprising administering a protease or peptidase inhibitor.

Meezan discloses that preferred **glycosides include maltose, sucrose, and glucose linked by a glycosidic linkage to an alkyl chain of 9, 10, 12, or 14 carbon atoms** (col. 6, lines 46-51). Compounds who absorption can be increased by Meezan's invented method include **peptide hormones (e.g. insulin, calcitonin, enkephalins, glucagon), hypoglycemic agents (e.g. tolbutamide and glyburide**), and agents which are poorly absorbed by enteric routes (e.g. friseofulvin) (col. 5, lines 17-32).

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the same composition, these must have the same properties, because a compound or composition and its properties may not be separated

Claims 1-13, 17-19, 23-27, 39, 43, and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Meezan et al. (U.S. Patent No. 5,817,634).

Applicants' claims have been described above.

Meezan discloses methods of treating diabetes mellitus and glycogen storage disease comprising administering a priming amount of a membrane-penetrating alkyl glycoside (title, abstract, claims). Preferred **glycosides include maltose, maltotriose, and maltotetraose linked by a glycosidic linkage to an alkyl chain of 8, 10, 12, or 14 carbon atoms** (col. 7, lines 45-51). The compositions may also comprise additional antidiabetes agents (e.g. proglycosyn, tolbutamide, glyburide, or acarabose) (col. 8, lines 33-39). The compounds or compositions are **preferably administered orally**, but may also be administered parenterally, by intramuscular injection, topically, by inhalation, or transdermally. These pharmaceutical compounds or compositions may be in the form of

solid, semi-solid, or liquid dosage forms, including tablets, granules, pills, capsules, etc. (col. 8, lines 40-43 and 54-63). Tablets and granules may be coated (col. 9, lines 34-35).

As was stated above, properties of the claimed surfactant or therapeutic compositions are inherent to these compositions. Wherein the prior art discloses the same composition, these must have the same properties, because a compound or composition and its properties may not be separated

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-13 and 45-46 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The cited claims read on the following compounds: (1) any alkyl glycoside and (2) any saccharide alkyl ester. Applicants' did not invent alkyl glycosides or saccharide alkyl esters, as evidenced, for example, by the disclosures of Hovgaard cited above; the disclosures of Nag (US 2003/0118594) in paragraph [0024]; and applicants' own admissions in the specification in paragraphs [0054]-[0056] and [0069]. Claims 45-46 are included with the presumption that these claims were intended to claim compositions and not methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meezan et al. (U.S. Patent No. 5,661,130) ("Meezan '130") in view of Crotts et al. (US 2003/0017203).

Note: In favor of compact prosecution and in anticipation of Applicants' claim amendments claims 1-22, 24-43 and 45-46 have been included in this rejection.

Applicant Claims

Applicants' claim the method of claim 31 wherein the composition is further comprised of an enteric coating.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meezan '130 have been set forth above in the instant office action. Crotts teaches an oral peptide pharmaceutical dosage form for the oral delivery of a peptide composition that includes an absorption enhancer effective to promote the bioavailability of the peptide and an **enteric coating** (title; abstract; claims 1 and 16-17). Crotts teaches that the invention is suitable for patients who suffer from disorders or diseases that are treatable by administration of a peptide [0013]. Suitable enteric coatings are described in [0034]-[0036]. Crotts focuses on the administration of calcitonin ([0013]; claims).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meezan '130 lacks the teaching of a composition further comprising an enteric coating. This deficiency is cured by the teachings of Crotts.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Meezan '130 and Crotts, because

Meezan teaches compositions comprising absorption enhancers and the same active agent (i.e. calcitonin) taught as being the active peptide in Crotts compositions. An ordinary skilled artisan would have been motivated to combine the teachings of Meezan '130 and Crotts because Crotts teaches that the invented compositions comprise absorption enhancers and can comprise any peptide that is useful in the treatment of a disease or condition, such as calcitonin, and Meezan teaches calcitonin compositions comprising alkyl glycoside absorption enhancers. An ordinary skilled artisan would have been further motivated to combine the teachings of Meezan and Crotts, because the presence of an enteric coating in Crotts compositions when combined with the teachings of Meezan '130 would enable the oral administration of calcitonin and other active peptide formulations. Because the enteric coating of Crotts compositions would be expected to prevent the degradation of peptide active agents, such as calcitonin or insulin, an ordinary skilled artisan would have had a reasonable expectation of success upon modification of the teachings of Meezan with the teachings of Crotts.

Relevant Terminal Disclaimers in Related Copending Applications

The terminal disclaimer filed on November 6, 2006 disclaiming the terminal portion of any patent granted on application No. 11/202,849, which would extend beyond the expiration date of copending application 11/127,786 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on July 6, 2006 disclaiming the terminal portion of any patent granted on application No. 11/219,337, which would extend beyond the

expiration date of copending application 11/127,786 has been reviewed and is accepted.

The terminal disclaimer has been recorded.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 14-17, 20-23, 31, 40-42, 43, and 45-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-10 of U.S. Patent No. 5,661,130 (USPN '130). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope and mutually obvious. It is noted that the cited claims of USPN '130 are drawn to methods of increasing absorption of a compound into the circulatory system comprising administration of a compound and an absorption increasing amount of a suitable non-toxic, nonionic alkyl glycoside. It is noted that

dependent claims 8-10 of USPN '130 specify that the compound in the composition is a protein or peptide, such as insulin and glucagon, and/or method further comprises the administration of a protease or peptidase inhibitor. The compositions utilized in the claimed methods of USPN '130 obviate the cited composition claims of the instant application. Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that claims of the instant application are *prima facie* obvious over claims 1-10 of USPN '130.

Claims 1, 8, 11, 31, and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825). Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims are substantially overlapping in scope and mutually obvious. Independent claim 1 of copending '825 claims a method of administering an alkyl saccharide composition comprising administering at least one alkyl saccharide having an alkyl chain length from 12 to about 14 carbon atoms and at least one saccharide moiety with antibacterial activity, at least one therapeutic agent and at least one enhancing agent. The term alkyl saccharide reads on alkyl glycoside. Independent claim 1 of the instant application claims a surfactant composition comprising at least one alkyl glycoside and/or at least one saccharide alkyl ester that when admixed with a drug stabilizes the biological activity and increases the bioavailability of the drug. Saccharide alky ester reads on enhancer. It is obvious from the wording of claim 1 of the instant application that the surfactants are intended to be mixed with a drug. Therefore, claim 1 of the

instant application is obviated by the composition utilized in claim 1 of copending '825. Independent claim 31 of the instant application claims a method of administering a drug composition comprising a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alky has from about 10 to about 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug. The term "delivered" reads on administering. Both claims 11 and 43 state that the surfactant composition of the instant application is formulated for mucosal delivery. Mucosal delivery reads on "transmucosal delivery." In conclusion, an ordinary skilled artisan would have concluded that claims 1, 8, 11, 31, and 43 of the instant application are prima facie obvious over claims 1-6 and 12-13 of copending Application No. 11/193,825 (copending '825).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Other Matter

The Examiner respectfully suggests amending claim 44, line 1 to read "further comprises" instead of "further comprised" to improve the readability of said claim and maintain agreement between the tense of "is" and "comprised".

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following references are relevant because these teach alkyl glycoside and/or saccharide alkyl ester compositions, including therapeutic compositions

and methods or use thereof: 2003/0118547; 5,268,461; 5,308,531; 5,639,733; 5,795,896; 4,921,838; 5,550,220; 200/0130260; 5,268,461; 5,192,528; 6,254,854; 2003/0158206; 6,482,834.

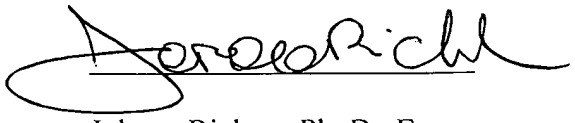
Claims 1-46 are rejected. The drawings, specification, and claims 1 and 17 are objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1636

PTO
JUL 25 2006
PATENT AND TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
JHA	AA	6,524,557 B1	02/25/2003	Backstrom et al.			
	AB	2003/0100755 A1	05/29/2003	Sham et al.			
	AC	2003/0118594 A1	06/26/2003	Nag et al.			
	AD	2004/0115135 A1	06/17/2004	Quay			
	AE	2004/0126358 A1	07/01/2004	Warne et al.			
	AF	2004/0147473 A1	07/29/2004	Warrell, Jr.			
JHA	AG	2005/0234101 A1	10/20/2005	Stenkamp et al.			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

EXAMINER	DATE CONSIDERED
	2/2/07

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449

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	Applicant: Meezan et al.	
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U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
[illegible]	AA	5,369,095	11/29/1994	Kee and Shaw			
[illegible]	AB	2002/0110524 A1	08/15/2002	Cowan, Siu Man L.			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)
[illegible]	AC	1-151528	06/14/1989	Japan			

Engl. Abs. and Claims only

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

EXAMINER	DATE CONSIDERED
[signature]	2/2/07

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
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U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
JHHA	AA	5,661,130	08/26/1997	Meezan and Pillion			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

JHHA	AB	Hovgaard, Lars et al., "Stabilization of insulin by alkylmaltosides. A. Spectroscopic evaluation", *International Journal of Pharmaceutics*, **Vol. 132, 107-113**, 1996
JHHA	AC	Hovgaard, Lars et al., "Stabilization of insulin by alkylmaltosides. B. Oral absorption in vivo in rats", *International Journal of Pharmaceutics,* **Vol 132, 115-121,** 1996
JHHA	AD	Tsuchido, Tetsuaki et al., "Lysis of Bacillus subtilis Cells by Glycerol and Sucrose Esters of Fatty Acids", *Applied and Environmental Microbiology,* **Vol. 53, No. 3, 505-508,** 1987
JHHA	AE	Watanabe, Takashi et al., "Antibacterial Carbohydrate Monoesters Suppressing Cell Growth of Streptoccus mutans in the Presence of Sucrose", *Current Microbiology,* **Vol. 41, 210-213,** 2000

EXAMINER GT\6465702.1 356897-183	DATE CONSIDERED 2/2/07

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449 1

Notice of References Cited	Application/Control No. 11/127,786	Applicant(s)/Patent Under Reexamination MEEZAN ET AL.	
	Examiner James H. Alstrum-Acevedo	Art Unit 1616	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,817,634	10-1998	Meezan et al.	514/24
*	B	US-3,849,341	11-1974		510/471
*	C	US-2003/0017203	01-2003	Crotts et al.	424/477
*	D	US-2003/0118547	06-2003	Vandenberg, Grant William	424/85.4
*	E	US-5,268,461	12-1993	Shoji et al.	536/41
*	F	US-5,308,531	05-1994	Urfer et al.	510/434
*	G	US-5,639,733	06-1997	Koike et al.	514/25
*	H	US-5,795,896	08-1998	Lofroth et al.	514/256
*	I	US-4,921,838	05-1990	Catsimpoolas et al.	514/25
*	J	US-5,550,220	08-1996	Meyer et al.	536/18.5
*	K	US-2005/0130260	06-2005	Linden et al.	435/068.1
*	L	US-5,268,461	12-1993	Shoji et al.	536/41
*	M	US-5,192,528	03-1993	Radhakrishnan et al.	424/45

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Beam et al. "Blood, Brain, Cerebrospinal Fluid Concentrations of Several Antibiotics in Rabbits with Intact and Inflamed Meninges," Antimicrobial Agents and Chemotherapy, 1977 (Dec.), 12(6), pp 710-716.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 11/127,786	Applicant(s)/Patent Under Reexamination MEEZAN ET AL.	
	Examiner James H. Alstrum-Acevedo	Art Unit 1616	Page 2 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,254,854	07-2001	Edwards et al.	424/46
*	B	US-2003/0158206	08-2003	Billotte et al.	514/252.16
*	C	US-6,482,834	11-2002	Spada et al.	514/311
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent under Reexamination
	11/127,786	MEEZAN ET AL.
	Examiner: James H. Alstrum-Acevedo	Art Unit: 1616

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	2/4/07
	1	O√
	2	√
	3	√
	4	√
	5	√
	6	√
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	9	√
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	11	√
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Bib Data Sheet

CONFIRMATION NO. 5393

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/127,786	05/11/2005 RULE	424	1616	AEGIS1210

APPLICANTS

Elias Meezan, Birmingham, AL;
Dennis J. Pillion, Hoover, AL;
Edward T. Maggio, San Diego, CA;

**** CONTINUING DATA ***************************

This appln claims benefit of 60/649,958 02/03/2005 and claims benefit of 60/637,284 12/17/2004
and claims benefit of 60/632,038 11/30/2004
and claims benefit of 60/609,890 09/14/2004
and claims benefit of 60/604,296 08/25/2004

**** FOREIGN APPLICATIONS ********************** NONE

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 06/10/2005

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☒ no	AL	3	46	3
35 USC 119 (a-d) conditions met ☐ yes ☒ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

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TITLE
Absorption enhancers for drug administration

FILING FEE RECEIVED	FEES: Authority has been given in Paper
1215	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

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- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
- ☐ Other _____
- ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination
	11/127,786	MEEZAN ET AL.
	Examiner	Art Unit
	James H. Alstrum-Acevedo	1616

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
PALM Inventor Name Search	1/31/2007	JHAA
EAST Citation Search of USPN 5369095	2/1/2007	JHAA
WEST Keyword Inventor Searches (USPN, PGPB, USOC, EPAB, JPAB, DWPI, TDBD)	2/1/2007	JHAA
STN Keyword Search (CAPLUS, MEDLINE, USPATFULL)	2/2/2007	JHAA
WEST Keyword Search (USPN, PGPB)	2/3/2007	JHAA

Freeform Search

Database: US Pre-Grant Publication Full-Text Database
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EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Term: L3 and ((insulin or calcitonin or tolbutamide) same (enter$4))

Display: 20 **Documents in Display Format:** CIT **Starting with Number** 1

Generate: Hit List Hit Count Side by Side Image

Search Clear Interrupt

Search History

DATE: Saturday, February 03, 2007 Purge Queries Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB; PLUR=YES; OP=OR			
L7	L3 and ((insulin or calcitonin or tolbutamide) same (enter$4))	16	L7
DB=USPT; PLUR=YES; OP=OR			
L6	5661130.pn.	1	L6
DB=PGPB; PLUR=YES; OP=OR			
L5	5661130.pn.	0	L5
DB=USPT; PLUR=YES; OP=OR			
L4	L3	3519	L4
DB=PGPB,USPT; PLUR=YES; OP=OR			
L3	L2 and @pd<20030825	4493	L3
L2	L1 same (enter$3 near8 (coat$4 or film))	8291	L2
L1	oral$4 same tablet	110415	L1

END OF SEARCH HISTORY

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     (FILE 'HOME' ENTERED AT 18:06:18 ON 02 FEB 2007)

     FILE 'CAPLUS, MEDLINE, USPATFULL' ENTERED AT 18:10:48 ON 02 FEB 2007
L1          2137 S ((ALKYL(W)GLYCOSIDE) OR (ALKYL(6A)GLYCOSIDE) OR (SACCHARIDE(W
L2           662 S L1 (P) (SURFACTANT OR (SURFACE(2A)ACTIVE(2A)AGENT) OR (SURFAC
L3             6 S L2 (P) ((NON(2A)IRRITANT) OR ANTIBACTERIAL OR (ANTI(2A)BACTER
L4             6 DUPLICATE REMOVE L3 (0 DUPLICATES REMOVED)
L5             6 FOCUS L4 1-
L6          1327 S (ALKYL(W)GLYCOSIDE)
L7             6 S ((SACCHARIDE(W)ALKYL(W)ESTER) OR (((DI OR TRI OR POLY OR OLIG
L8             5 DUPLICATE REMOVE L7 (1 DUPLICATE REMOVED)
L9           520 S L6 (P) (SURFACTANT OR (SURFACE(2A)ACTIVE(2A)AGENT) OR (SURFA
L10            4 S L7 (P) ((NON(2A)IRRITANT) OR ANTIBACTERIAL OR (ANTI(2A)BACTE
L11            4 DUPLICATE REMOVE L10 (0 DUPLICATES REMOVED)
L12           48 S L9 (P) (DRUG OR PHARMACEUTICAL OR MEDICAMENT OR (ACTIVE(W)AG
L13           45 DUPLICATE REMOVE L12 (3 DUPLICATES REMOVED)
L14           45 FOCUS L13 1-

     FILE 'STNGUIDE' ENTERED AT 18:33:57 ON 02 FEB 2007

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L1          2137 SEA ((ALKYL(W) GLYCOSIDE) OR (ALKYL(6A) GLYCOSIDE) OR (SACCHARI
                 DE(W) ALKYL(W) ESTER) OR (((DI OR TRI OR POLY OR OLIGO)(3A)
                 SACCHARIDE)(8A)(ALKYL(8A) ESTER)))


=> d que l2
L1          2137 SEA ((ALKYL(W) GLYCOSIDE) OR (ALKYL(6A) GLYCOSIDE) OR (SACCHARI
                 DE(W) ALKYL(W) ESTER) OR (((DI OR TRI OR POLY OR OLIGO)(3A)
                 SACCHARIDE)(8A)(ALKYL(8A) ESTER)))
L2           662 SEA L1 (P) (SURFACTANT OR (SURFACE(2A) ACTIVE(2A) AGENT) OR
                 (SURFACE-ACTIVE(2A) AGENT) OR DETERGENT)


=> dque l3
DQUE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d que l7
L7             6 SEA ((SACCHARIDE(W) ALKYL(W) ESTER) OR (((DI OR TRI OR POLY OR
                 OLIGO)(3A) SACCHARIDE)(8A)(ALKYL(8A) ESTER)))


=> d que l9
L6          1327 SEA (ALKYL(W) GLYCOSIDE)
L9           520 SEA L6 (P) (SURFACTANT OR (SURFACE(2A) ACTIVE(2A) AGENT) OR
                 (SURFACE-ACTIVE(2A) AGENT) OR DETERGENT)


=> d que l10
L7             6 SEA ((SACCHARIDE(W) ALKYL(W) ESTER) OR (((DI OR TRI OR POLY OR
                 OLIGO)(3A) SACCHARIDE)(8A)(ALKYL(8A) ESTER)))
L10            4 SEA L7 (P) ((NON(2A) IRRITANT) OR ANTIBACTERIAL OR (ANTI(2A)
                 BACTERIAL))


=> d que l12
L6          1327 SEA (ALKYL(W) GLYCOSIDE)
L9           520 SEA L6 (P) (SURFACTANT OR (SURFACE(2A) ACTIVE(2A) AGENT) OR
                 (SURFACE-ACTIVE(2A) AGENT) OR DETERGENT)
L12           48 SEA L9 (P) (DRUG OR PHARMACEUTICAL OR MEDICAMENT OR (ACTIVE(W)
                 AGENT) OR THERAPEUTIC OR BIOACTIVE OR PROTEIN OR PEPTIDE OR
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ENZYME OR HORMONE)

L5 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
TI Kitchen cleaning composition with less skin chapping
AB Title composition, suitable for cleaning sponges, chopping boards, dishes, vegetables, and fruits, etc., comprises (A) alkyl glycoside 5-80, (B) N-containing nonionic surfactant 1-50, (C) polylysine 0.0001-1, and (D) chelating agent 0.01-5 wt%. Thus, a cleaning agent comprising an alkyl glycoside 10, dodecyl di-Me amine oxide 2, palm-kernel fatty acid diethanolamide 3, ε-polylysine 0.5, Na citrate 0.5, and H2O showed good foaming ability, cleaning power, antibacterial effect against Escherichia coli and Staphylococcus aureus, and hand-chapping degree 4.

ACCESSION NUMBER: 2000:60064 CAPLUS
DOCUMENT NUMBER: 132:109803
TITLE: Kitchen cleaning composition with less skin chapping
INVENTOR(S): Takano, Katsuyuki; Maruta, Kazunari; Ide, Kazutoshi
PATENT ASSIGNEE(S): Kao Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000026889	A	20000125	JP 1998-191346	19980707

PRIORITY APPLN. INFO.: JP 1998-191346 19980707
OTHER SOURCE(S): MARPAT 132:109803

L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
TI Liquid composition, its preparation and application
AB The liquid composition is composed of polyvinylpyrrolidone 1- 3, hydroxypropyl Me cellulose 0.5-5, Na alginate 1-3, trichlorohydroxydiphenyl ether or chlorhexidine acetate 0.1-0.5, surfactant (Na dodecyl sulfate, polyoxyethylene nonylphenyl ether, and/or C20 alkyl glycoside) 4.0-15.0, glycerol 3-10, EDTA-Na2 0.1-0.2, and urea 0.1-1.0%, and its pH 6.0-7.0. The liquid composition may be used to form the antibacterial film on skin.

ACCESSION NUMBER: 2005:295792 CAPLUS
DOCUMENT NUMBER: 142:322810
TITLE: Liquid composition, its preparation and application
INVENTOR(S): Wang, Yu
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 12 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1457764	A	20031126	CN 2003-135174	20030610

PRIORITY APPLN. INFO.: CN 2003-135174 20030610

L5 ANSWER 3 OF 6 USPATFULL on STN
TI Antibacterial compositions for drug administration
AB An antibacterial composition having at least one alkyl glycoside, at least one saccharide, and at least one therapeutic agent, wherein the alkyl glycoside has an alkyl chain length from about 12 to about 14 carbon atoms and wherein the saccharide has antibacterial activity, thereby providing for a composition having antibacterial activity.

ACCESSION NUMBER: 2006:54664 USPATFULL
TITLE: Antibacterial compositions for drug administration
INVENTOR(S): Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): Aegis Therapeutics LLC, San Diego, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006046969	A1	20060302
APPLICATION INFO.:	US 2005-193825	A1	20050729 (11)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DLA PIPER RUDNICK GRAY CARY US, LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2042
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 6 USPATFULL on STN
TI Absorption enhancers for drug administration
AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

ACCESSION NUMBER: 2006:54657 USPATFULL
TITLE: Absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias, Birmingham, AL, UNITED STATES
Pillion, Dennis J., Hoover, AL, UNITED STATES
Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): Aegis Therapeutics LLC, San Diego, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006046962	A1	20060302
APPLICATION INFO.:	US 2005-127786	A1	20050511 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DLA PIPER RUDNICK GRAY CARY US, LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133, US

NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1970
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 6 USPATFULL on STN
TI Absorption enhancers for drug administration
AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.
ACCESSION NUMBER: 2006:53568 USPATFULL
TITLE: Absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias, Birmingham, AL, UNITED STATES
Pillion, Dennis J., Hoover, AL, UNITED STATES
Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): AEGIS THERAPEUTICS LLC (U.S. corporation)
THE UAB RESEARCH FOUNDATION (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006045869	A1	20060302
APPLICATION INFO.:	US 2005-219337	A1	20050901 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPER RUDNICK GRAY CARY US LLP, 4365 Executive Drive, Suite 1100, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1-86
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2029
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 6 USPATFULL on STN
TI Absorption enhancers for drug administration
AB A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.
ACCESSION NUMBER: 2006:53567 USPATFULL
TITLE: Absorption enhancers for drug administration
INVENTOR(S): Meezan, Elias, Birmingham, AL, UNITED STATES
Pillion, Dennis J., Hoover, AL, UNITED STATES
Maggio, Edward T., San Diego, CA, UNITED STATES

PATENT ASSIGNEE(S): AEGIS THERAPEUTICS LLC (U.S. corporation)
THE UAB RESEARCH FOUNDATION (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006045868	A1	20060302
APPLICATION INFO.:	US 2005-202849	A1	20050812 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPER RUDNICK GRAY CARY US LLP, Suite 1100, 4365 Executive Drive, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1-46
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1964
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 5 USPATFULL on STN
TI Therapeutic Peptides and Vaccines
AB Compositions are disclosed that induce broadly HIV theraputic and vaccine inducing antibodies against diverse HIV clades and relate to the ability to identify HIV gp120-derived short peptide sequence immunogens and various therapeutic compositions made from the identified peptides which compose CCR5 binding sites. Also disclosed are methods of selecting peptide sequences that are likely candidates for drugs which will offer effective treatment in such areas as Alzheimer's disease, psoriasis, multiple sclerosis and other diseases associated with the human inflammatory cascade as well as related retroviruses such as HTLV-1, the cause of tropical spastic paraparesis.

ACCESSION NUMBER:	2006:340387 USPATFULL		
TITLE:	Therapeutic Peptides and Vaccines		
INVENTOR(S):	Ruff, Michael, Potomac, MD, UNITED STATES		
	Pert, Candace, Potomac, MD, UNITED STATES		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006292167	A1	20061228	
APPLICATION INFO.:	US 2006-426301	A1	20060623	(11)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2005-693087P	20050623	(60)
	US 2005-693088P	20050623	(60)
	US 2005-693089P	20050623	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	KILE GOEKJIAN REED & MCMANUS, 1200 NEW HAMPSHIRE AVE, NW, SUITE 570, WASHINGTON, DC, 20036, US
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Page(s)
LINE COUNT:	1081

L14 ANSWER 1 OF 45 CAPLUS COPYRIGHT 2007 ACS on STN
TI Liquid detergent composition containing combination of enzymes
AB The title composition contains a protease, an amylase, a cellulase, and an alkyl glycoside surfactant and shows good enzyme stability during storage and good detergency. A composition contained fatty acid 5, ethoxylated fatty alcs. 20, alkyl glycoside 20, alkyl sulfate 4.6, EtOH 5, 1,2-propanediol 8, protease 1, amylase 0.5, cellulase 1, perfume 1, monoglyceride 0.5, and water 24.4%.

ACCESSION NUMBER: 1995:863394 CAPLUS
DOCUMENT NUMBER: 123:260464
TITLE: Liquid detergent composition containing combination of enzymes
INVENTOR(S): Meine, Georg
PATENT ASSIGNEE(S): Henkel K.-G.a.A., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4339382	A1	19950524	DE 1993-4339382	19931118
WO 9514074	A1	19950526	WO 1994-EP3691	19941109
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 729502	A1	19960904	EP 1995-900124	19941109
EP 729502	B1	19990728		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL				
AT 182616	T	19990815	AT 1995-900124	19941109
ES 2136270	T3	19991116	ES 1995-900124	19941109

PRIORITY APPLN. INFO.: DE 1993-4339382 A 19931118
WO 1994-EP3691 W 19941109

L14 ANSWER 2 OF 45 CAPLUS COPYRIGHT 2007 ACS on STN
TI Alkyl glycoside detergents: synthesis and applications to the study of membrane proteins
AB An improved synthesis of the detergent laurylmaltoside is described, which uses higher levels of dodecanol to increase the yield. The method is applicable to preparation of other alkyl glycoside detergents. The detergent can be used to disperse heart cytochrome C and photosynthetic centers from Rhodopseudomonas sphaeroides.

ACCESSION NUMBER: 1986:494078 CAPLUS
DOCUMENT NUMBER: 105:94078
TITLE: Alkyl glycoside detergents: synthesis and applications to the study of membrane proteins
AUTHOR(S): VanAken, T.; Foxall-VanAken, S.; Castleman, S.; Ferguson-Miller, S.
CORPORATE SOURCE: BonSecours Hosp., Grosse Pointe, MI, 48230, USA
SOURCE: Methods in Enzymology (1986), 125(Biomembranes, Pt. M), 27-35
CODEN: MENZAU; ISSN: 0076-6879
DOCUMENT TYPE: Journal
LANGUAGE: English

L14 ANSWER 4 OF 45 USPATFULL on STN
TI Conditioning and detergent compositions and use
AB The present invention relates to a conditioning and detergent cosmetic composition for keratinous substances comprising, in an aqueous medium:

(A) at least one non-volatile vegetable oil,

(B) at least one anionic sulphate surface-active agent,

(C) at least one non-ionic alkyl glycoside surface-active agent, the (B)/(C) ratio by weight being less than or equal to 2:1.

Use in simultaneously caring for and washing keratinous substances, in particular the hair.

ACCESSION NUMBER: 2000:164057 USPATFULL
TITLE: Conditioning and detergent compositions and use
INVENTOR(S): Maurin, Veronique, Paris, France
Mellul, Myriam, L'Hay les Roses, France
Beauquey, Bernard, Clichy, France
PATENT ASSIGNEE(S): L'Oreal, S.A., Paris, France (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6156297		20001205	
APPLICATION INFO.:	US 1999-338864		19990623	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1998-8007	19980624

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Queeney, P. M.
LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 683
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 6 OF 45 CAPLUS COPYRIGHT 2007 ACS on STN
TI Cosmetic and pharmaceutical aerosol foams containing alkyl glycosides
AB Cosmetic and topical pharmaceutical aerosol foams comprise an aqueous phase containing a water-soluble polymer, a water-soluble alkyl (oligo)glycoside surfactant, and a propellant. Thus, an aerosol shaving cream contained Edenor K8-18 (coco fatty acids) 10.00, PEG (mol. weight 1550) 5.10, Collapurol E1 [1 weight% soluble collagen partially esterified with EtOH in H2O-EtOH (80:20)] 0.03, NaOH 2.50, Plantaren 1200 0.70, Merquat 550 0.20, Drivosol 27 (propellant) 9.60, and water to 100.00 weight%.

ACCESSION NUMBER: 1995:471866 CAPLUS
DOCUMENT NUMBER: 122:222470
TITLE: Cosmetic and pharmaceutical aerosol foams containing alkyl glycosides
INVENTOR(S): Seidel, Kurt; Hollenberg, Detlef; Kaczich, Anke; Priebe, Christian
PATENT ASSIGNEE(S): Henkel K.-G.a.A., Germany
SOURCE: Ger. Offen., 15 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4327699	A1	19950223	DE 1993-4327699	19930819
WO 9505158	A1	19950223	WO 1994-EP2647	19940810

W: CA, CN, CZ, JP, KR, PL, RU, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: DE 1993-4327699 A 19930819

L14 ANSWER 9 OF 45 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of alkyl oligosaccharide glycosides and acetyl derivatives thereof
AB The title glycosides, useful as intermediates for surfactants or medicines, are prepared by glycosidation of peracetate derivs. of (1→4)-β-oligoglucosides, 4' O-β-galactosyllactose, or 4'-O-β-[(1→4)-β-oligogalactosyl]lactose with alcs. in the presence of an acid, e.g., heteropoly acid. Thus, acetylation of laminaripentaose by Ac2O in the presence of AcONa under reflux for 1 h and condensation of the resulting β-D-laminaripentaose peracetate with n-dodecyl alc. in the presence of FeCl3 in toluene at 90° for 1.5 h gave n-dodecyl β-D-laminaripentaoside peracetate.

ACCESSION NUMBER: 1992:408360 CAPLUS
DOCUMENT NUMBER: 117:8360
TITLE: Preparation of alkyl oligosaccharide glycosides and acetyl derivatives thereof
INVENTOR(S): Shoji, Tadao; Takahashi, Nahoko; Adachi, Koichiro; Ikushima, Naoya; Katsuraya, Kaname; Uryu, Toshiyuki; Yoshida, Takashi
PATENT ASSIGNEE(S): Dainippon Ink Chemical Industry Co., Japan
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9200310	A1	19920109	WO 1991-JP867		19910627
W: AU, CA, JP, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE					
CA 2065265	A1	19911228	CA 1991-2065265		19910627
AU 9180783	A	19920123	AU 1991-80783		19910627
AU 638146	B2	19930617			
EP 491960	A1	19920701	EP 1991-911967		19910627
EP 491960	B1	19960320			
R: CH, DE, FR, GB, IT, LI					
US 5268461	A	19931207	US 1992-834305		19920225
PRIORITY APPLN. INFO.:			JP 1990-169551	A	19900627
			JP 1990-169552	A	19900627
			JP 1990-203719	A	19900731
			WO 1991-JP867	A	19910627

L14 ANSWER 11 OF 45 USPATFULL on STN
TI Composition for oral cavity
AB The present invention provides an oral composition comprising crystalline cellulose, and one or more surface active agents selected from the group consisting of alkyl glycoside, polyglycerin fatty acid ester, sucrose fatty acid ester and betaine, which has an excellent shape-holding ability and dispersibility in an oral cavity, does not change a taste of juice after teeth brushing, in addition, has excellent stability with time not causing solid-liquid separation. Moreover, the present invention provides an oral composition comprising a cationic bactericide and crystalline cellulose, which can effectively prevent an oral cavity disease such as a periodontal disease, dental caries and the like by enhancing an ability of the cationic bactericide to reside on a tooth surface.

ACCESSION NUMBER: 2005:280404 USPATFULL
TITLE: Composition for oral cavity
INVENTOR(S): Nakao, Akira, Osaka, JAPAN
Saito, Toru, Osaka, JAPAN
PATENT ASSIGNEE(S): SUNSTAR KABUSHIKI KAISHA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005244346	A1	20051103	
APPLICATION INFO.:	US 2003-517053	A1	20020607	(10)
	WO 2002-JP5639		20020607	
			20050706	PCT 371 date

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Stephen B Maebius, Foley & Lardner, Suite 500, 3000 K Street NW, Washington, DC, 20007-5109, US
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 958
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 13 OF 45 USPATFULL on STN
TI Nonionic surface active agent
AB A nonionic surface active agent comprising a fatty acid ester of a hexose sugar or an alkyl glycoside thereof, wherein the content of monoester is from 93 to 99.9% by weight, the content of diester is from 0.1 to 7% by weight and the content of tri- and higher polyesters is from 0 to 1% by weight in the fatty acid ester.
ACCESSION NUMBER: 92:34283 USPATFULL
TITLE: Nonionic surface active agent
INVENTOR(S): Sekiguchi, Shizuo, Funabashi, Japan
Yasumasu, Tomoko, Funabashi, Japan
Miyake, Hiroshi, Narashino, Japan
Endo, Yoshihisa, Sakura, Japan
PATENT ASSIGNEE(S): Lion Corporation, Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5109127		19920428	
APPLICATION INFO.:	US 1990-608738		19901105	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1989-288154	19891106

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Griffin, Ronald W.
ASSISTANT EXAMINER: Leary, Louise
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 1639
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 15 OF 45 USPATFULL on STN
TI Antibacterial compositions for drug administration
AB An antibacterial composition having at least one alkyl glycoside, at least one saccharide, and at least one therapeutic agent, wherein the alkyl glycoside has an alkyl chain length from about 12 to about 14 carbon atoms and wherein the saccharide has antibacterial activity, thereby providing for a composition having antibacterial activity.
ACCESSION NUMBER: 2006:54664 USPATFULL
TITLE: Antibacterial compositions for drug administration
INVENTOR(S): Maggio, Edward T., San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): Aegis Therapeutics LLC, San Diego, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2006046969 A1 20060302
APPLICATION INFO.: US 2005-193825 A1 20050729 (11)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2005-127786, filed on 11 May 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-649958P	20050203 (60)
	US 2004-637284P	20041217 (60)
	US 2004-632038P	20041130 (60)
	US 2004-609890P	20040914 (60)
	US 2004-604296P	20040825 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DLA PIPER RUDNICK GRAY CARY US, LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2042
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 19 OF 45 CAPLUS COPYRIGHT 2007 ACS on STN
TI Surfactant mixtures for shampoos containing alkyl glycosides
AB A surfactant mixture for washing the hair which is nonirritant to the skin contains (a) anionic surfactant 1-50, (b) alkyl glycoside 0.5-15, (c) synthetic nonionic polymer 0.1-7, and (d) water 28-98.4 weight%. Thus, a composition containing 28% aqueous Na lauryl ether sulfate solution 9.0, 22% aqueous Akypo-Soft 100NV (ethoxylated AcONa alkyl ether) solution 3.0, 30% aqueous Dehyton K (coco amidopropylbetaine) solution 3.0, Nutrilan (protein hydrolyzate) 0.5, PVP (nonionic polymer) 1.0, APG 600 (fatty alc. glucoside, d.p. 1.45) 2.0, and water to 100 weight% conferred excellent dry combability, holding efficiency, skin compatibility, and foaming properties with low electrostatic charge.
ACCESSION NUMBER: 1994:612619 CAPLUS
DOCUMENT NUMBER: 121:212619
TITLE: Surfactant mixtures for shampoos containing alkyl glycosides
INVENTOR(S): Mueller, Reinhard; Seidel, Kurt; Hollenberg, Detlef; Ehlert, Manuela
PATENT ASSIGNEE(S): Henkel K.-G.a.A., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4302314	A1	19940804	DE 1993-4302314	19930128
WO 9416678	A1	19940804	WO 1994-EP132	19940120
W: BR, CA, JP, KR, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 681468	A1	19951115	EP 1994-905094	19940120
EP 681468	B1	19970319		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
AT 150295	T	19970415	AT 1994-905094	19940120
ES 2099592	T3	19970516	ES 1994-905094	19940120
PRIORITY APPLN. INFO.:			DE 1993-4302314 A	19930128
			WO 1994-EP132 W	19940120

L14 ANSWER 32 OF 45 USPATFULL on STN
TI Pine-oil containing hard surface cleaning composition
AB Concentrated hard surface cleaning compositions containing pine oil and/or terpenes and nonionic and a anionic surfactants can be obtained as clear liquids which remain clear when diluted with water.

ACCESSION NUMBER: 94:37629 USPATFULL
TITLE: Pine-oil containing hard surface cleaning composition
INVENTOR(S): Urfer, Allen D., Lansdale, PA, United States
Lazarowitz, Virginia L., Hatfield, PA, United States
PATENT ASSIGNEE(S): Henkel Corporation, Plymouth Meeting, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5308531		19940503	
APPLICATION INFO.:	US 1992-938734		19920831	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Skane, Christine
ASSISTANT EXAMINER: Hertzog, A.
LEGAL REPRESENTATIVE: Szoke, Ernest G., Jasechke, Wayne C., Drach, John E.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 267
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 44 OF 45 USPATFULL on STN
TI Antithrombotic formulation, process for its manufacturing, and use thereof
AB A new pharmaceutical formulation comprising the thrombin inhibitor HOOC--CH.sub.2 --(R)-Cgl-Aze-Pab in combination with one or more absorption enhancing agents, a process for the preparation of such a pharmacutical formulation, the use of such a formulation in the treatment of thromboembolism as well as a method of treating a patient in need of antithrombotic treatment and thromboembolism by using said formulation.

ACCESSION NUMBER: 1998:98920 USPATFULL
TITLE: Antithrombotic formulation, process for its manufacturing, and use thereof
INVENTOR(S): Lofroth, Jan-Erik, Molndal, Sweden
Ungell, Anna-Lena, Goteborg, Sweden
PATENT ASSIGNEE(S): Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795896		19980818	
	WO 9616671		19960606	
APPLICATION INFO.:	US 1995-564122		19951218	(8)
	WO 1995-SE1425		19951129	
			19951218	PCT 371 date
			19951218	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1994-4196	19941202

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: MacMillan, Keith
LEGAL REPRESENTATIVE: Nixon & Vanderhye
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 537

L14 ANSWER 36 OF 45 USPATFULL on STN
TI Alkyl glycoside aqueous solution
AB Alkyl glycoside aqueous solutions, which satisfy the following conditions (a) and/or (b):

(a) the solution is maintained at a pH value exceeding 7, and

(b) the solution contains a water-soluble alcohol, are highly stable with respect to microbial activities, such as putrefaction and fungal growth, and are useful as surface active agents.

ACCESSION NUMBER: 97:51980 USPATFULL
TITLE: Alkyl glycoside aqueous solution
INVENTOR(S): Koike, Toyomi, Wakayama, Japan
Nagumo, Hiroshi, Wakayama, Japan
Yamamuro, Akira, Wakayama, Japan
Yokota, Yukinaga, Osaka, Japan
PATENT ASSIGNEE(S): Kao Corporation, Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5639733		19970617
APPLICATION INFO.:	US 1994-340351		19941114 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-207252, filed on 8 Mar 1994, now abandoned which is a continuation of Ser. No. US 1992-883679, filed on 15 May 1992, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1991-111589	19910516

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: White, Everett
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 392
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

EAST CITATION Search of 5,369,095

US 7128928 B2	USPAT
US 6630135 B1	USPAT
US 5985259 A	USPAT
US 5661130 A	USPAT
US 5631004 A	USPAT
US 5262178 A	USPAT
US 5219887 A	USPAT
US 5062989 A	USPAT
US 5041450 A	USPAT
US 4942038 A	USPAT
US 4923693 A	USPAT
US 4921838 A	USPAT
US 4742083 A	USPAT
US 4725590 A	USPAT
US 4722837 A	USPAT
US 4558063 A	USPAT
US 4237141 A	USPAT
US 4215130 A	USPAT

Freeform Search

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EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Term: L21 and ("alkyl glycoside" or "saccharide alkyl ester" or (saccharide near8 ("alkyl ester" or (alkyl near4 ester))))

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1

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	DB=PGPB,USPT; PLUR=YES; OP=OR		
L22	L21 and ("alkyl glycoside" or "saccharide alkyl ester" or (saccharide near8 ("alkyl ester" or (alkyl near4 ester))))	4	L22
L21	Edward near4 Maggio	133	L21
L20	Dennis near4 Pillion	6	L20
L19	Elias near Meezan	10	L19
	DB=EPAB; PLUR=YES; OP=OR		
L18	CN-1072677-C.did.	0	L18
	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
L17	L15 same L14	29	L17
L16	L15 and L14	51	L16
L15	$5saccharide near5 ester	3467	L15
L14	"alkyl glycoside"	2549	L14
L13	L12 and @pd<20030825	2003	L13
L12	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltosideor	3231	L12

	"myristyl maltoside" or myristylmaltoside) and @pd<20030825) same (surfactant or "surface active agent" or "surface-active agent"))		
L11	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltoside or "myristyl maltoside" or myristylmaltoside) and @pd<20030825) and surfactant)	6630	L11
L10	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltosideor "myristyl maltoside" or myristylmaltoside) and @pd<20030825 and surfactant) and (surfactant or "alkyl glycoside").ttl.)	0	L10
L9	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltosideor "myristyl maltoside" or myristylmaltoside) and @pd<20030825) and surfactant)	1562	L9
L8	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltosideor "myristyl maltoside" or myristylmaltoside)) and @pd<20030825)	15405	L8
L7	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM) and (TDM or "tetradecyl maltoside" tetradecylmaltosideor "myristyl maltoside" or myristylmaltoside))	25167	L7
L6	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltoside)) and ("alkyl ester" near8 ($5saccharide or carbohydrate or sugar or lactose or maltose or sucrose or glucose or fructose or $8tose)))	6	L6
L5	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltoside)) and ("alkyl ester" near8 ($5saccharide or carbohydrate or sugar or lactose or maltose or sucrose or glucose or fructose or $8tose)))	6	L5
L4	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM and (TDM or "tetradecyl maltoside" tetradecylmaltoside)) same ("alkyl ester" near8 ($5saccharide or carbohydrate or sugar or lactose or maltose or sucrose or glucose or fructose or $8tose)))	0	L4
L3	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM) and (TDM or "tetradecyl maltoside" tetradecylmaltoside))	25173	L3
L2	((((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM) same ("alkyl ester" near8 ($5saccharide or carbohydrate or sugar or lactose or maltose or sucrose or glucose or fructose or $8tose)))	24	L2
L1	(((tetradecyl or alkyl or dodecyl) near6 (maltoside or glycoside or sucroside or glucoside)) or TDM)	32236	L1

END OF SEARCH HISTORY

Inventor Name Search

Enter the **first few letters** of the Inventor's Last Name.
Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	First Name	
Maggio	Edward	Search

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Inventor Name Search

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Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	First Name	
Pillion	Dennis	Search

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: Bm. 1/1527 780

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))			150	150			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))				250			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))				100			
TOTAL CLAIMS (37 CFR 1.16(i))	46 minus 20 =	* 26	x 25 =	650	OR	x =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x =			x =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1150		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 46	Minus	** 46	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

OIPE IAP8
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PATENT & TRADEMARK OFFICE

IFW

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application please find:

1. Information Disclosure Statement (2 pgs.);
2. PTO Form 1449 (1 pg.);
3. Two references (Patent Abstract); and
4. Return Receipt Postcard.

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on August 29, 2006, in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Karen LePari

Karen LePari

GT\6502158.1
356894-12

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement, because it is being filed before the mailing of a first Office Action on the merits. However, if any fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of this Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 29, 2006

Liz Bui, Ph.D.
Reg. No.: 58,360
Telephone: (858) 638-6637
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO CUSTOMER NUMBER 28213

OIPE IAP8
SEP 01 2006
PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. § 1.97, enclosed are references relating to the above-identified application. For the convenience of the Examiner, the reference is listed on the attached Form PTO-1449. A copy of the non-patent document is enclosed herewith.

In accordance with 37 U.S.C. § 1.98(a)(2)(iv)(3)(1), Japanese Application No. 1-151528 appears to be relevant to the above-identified application for the following reason. The subject matter of the above-identified application is a pharmaceutical composition comprising an alkyl glycoside in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier. Japanese Application No. 1-151528 is directed to a (thio)ether compound of monosaccharides or disaccharides as an active component to obtain a transmucous absorbefacient.

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on August 29, 2006, in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Karen LePari

Karen LePari

GT\6502169.1
356894-12

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement, because it is being filed before the mailing of a first Office Action on the merits. However, if any fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 07-1896, referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 29, 2006

Liz Bui, Ph.D.
Registration No. 58,360
Telephone: (858) 638-6637
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NO. 28213

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1636

OIPE
SEP 01 2006
PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA	5,369,095	11/29/1994	Kee and Shaw			
	AB	2002/0110524 A1	08/15/2002	Cowan, Siu Man L.			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)
	AC	1-151528	06/14/1989	Japan			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form 1449

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356894-12

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 01-151528

(43)Date of publication of application : 14.06.1989

(51)Int.Cl. A61K 47/00
A61K 9/02

(21)Application number : 62-311680

(22)Date of filing : 08.12.1987

(71)Applicant : TAIHO YAKUHIN KOGYO KK

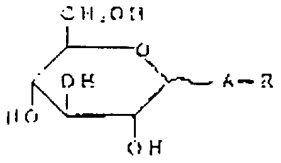
(72)Inventor : MURANISHI SHOZO

(54) TRANSMUCOUS ABSORBEFACIENT

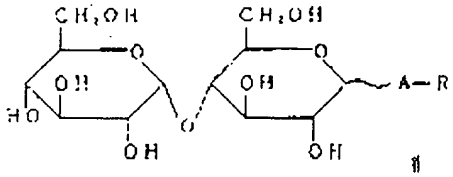
(57)Abstract:

PURPOSE: To obtain a transmucous absorbefacient for a hardly absorbable drug, by using a (thio)ether compound of monosaccharides or disaccharides as an active component.

CONSTITUTION: The objective transmucous absorbefacient contains an ether compound or thioether compound of monosaccharides (e.g. L-arabinose or D-mannose) or disaccharides (e.g. maltose) and a 6W18C aliphatic hydrocarbon, preferably a compound of formula I or formula II (A is O or S; R is 6W18C aliphatic hydrocarbon group). The amount of drug component in a mucous administration drug containing said absorbefacient is preferably 0.1W20wt.%, especially 0.5W5wt.%. The (thio)ether compound is e.g. n-octyl-β-D-(thio) glucopyranoside or n-lauryl-β-D-maltopyranoside.



I



II

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than

the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

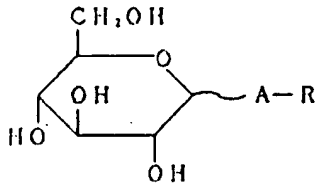
[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

CLAIMS

1. An agent for accelerating transmucosal absorption of a poorly absorbable drug, wherein the agent comprises one or more ether or thioether compounds of C_6-C_{18} aliphatic hydrocarbon and monosaccharide or disaccharide.

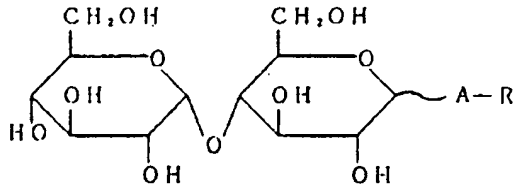
2. The agent of claim 1, wherein the ether or thioether compound of aliphatic hydrocarbon and monosaccharide is represented by Formula (1):



(1)

wherein A represents an oxygen atom or sulfur atom; and R represents a C_6-C_{18} aliphatic hydrocarbon group.

3. The agent of claim 1, wherein the ether or thioether compound of aliphatic hydrocarbon and disaccharide is represented by Formula (2):



(2)

wherein A represents an oxygen atom or sulfur atom; and R represents a C_6-C_{18} aliphatic hydrocarbon group.

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　平1－151528

⑤Int.Cl.⁴	識別記号	庁内整理番号	㊸公開　平成1年(1989)6月14日
A 61 K 47/00	326	E－7417－4C	
9/02		E－7417－4C	

審査請求　未請求　発明の数 1　（全6頁）

㊹発明の名称　経粘膜吸収促進剤

㉑特　願　昭62－311680

㉒出　願　昭62(1987)12月8日

特許法第30条第1項適用　昭和62年9月18日　日本薬剤学会発行の「日本薬剤学会第3年会講演要旨集」において発表

㉒発明者　村西　昌三　京都府京都市上京区烏丸通一条上ル西入ル観三橋町562－19

㉑出願人　大鵬薬品工業株式会社　東京都千代田区神田錦町1－27

㉔代理人　弁理士　田村　巌

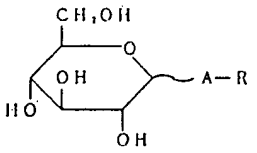
明　細　書

1．発明の名称　経粘膜吸収促進剤

2．特許請求の範囲

(1) 単糖類もしくは二糖類と炭素数6～18の脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物の1種以上を有効成分として含有する難吸収性薬物の経粘膜吸収促進剤。

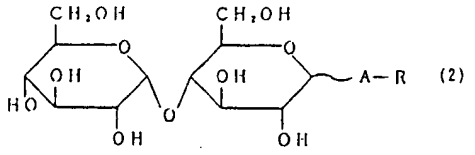
(2) 単糖類と脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物が下記一般式(1)で表わされる化合物である特許請求の範囲第1項記載の経粘膜吸収促進剤。



(1)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6～18の脂肪族炭化水素基を示す)

(3) 二糖類と脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物が下記一般式(2)で表わされる化合物である特許請求の範囲第1項記載の経粘膜吸収促進剤。



(2)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6～18の脂肪族炭化水素基を示す)

3．発明の詳細な説明

(産業上の利用分野)

本発明は新規な経粘膜吸収促進剤に関する。

(従来の技術)

吸収促進剤を含有する粘膜投与製剤の開発は、水溶性薬物や生理活性ペプチド等の難吸収性薬物を注射によらず有効に全身に適用するためのアプローチの1つとして注目されているが、実用に供した例は依然として少ない。理想的な吸収促進剤が具備すべき条件としては、強力かつ安全でまた安定であること、さらに製剤化した時にもその効力が損なわれず、主薬並びに製剤の安定性にも影響を与えないことなどが挙げられる。

粘膜からの吸収性を向上させるための研究は、従来より盛んに行われており、親水性界面活性剤の使用、脂肪酸類及びミセルの使用、エナミン誘導体、サリチル酸誘導体の添加等がある。(J. Pharm. Sci. 66 (7) 955 (1955); 薬剤学 38 (2) 67 (1978); Clin. Res. 25 (3) 386A; J. Pharm. Dyn. 3 24 (1980); Int. J. Pharm. 2 101 (1979); 特公昭55-8486; 特公昭55-8456; 特開昭57-158719; 特開昭58-177995; 特開昭59-176209等)。

しかしこれらの中には、組織粘膜を損傷したり、効果が不十分であったり、製剤化が困難である等の欠点を有するものが多く、より有効且つ安全で使用し易い吸収促進剤の開発が期待されている。

(発明が解決しようとする問題点)

本発明の目的は、より効果が強力で、安全且つ安定した経粘膜吸収促進剤を提供することにある。

(問題点を解決するための手段)

本発明は単糖類もしくは二糖類と炭素数6~18の脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物の1種以上を有効成分として含有する難吸収性薬物の経粘膜吸収促進剤に係る。

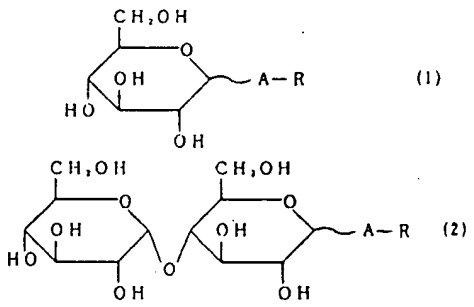
本発明者は有用な経粘膜吸収促進剤の開発を目的として鋭意研究を重ねた結果、実用上更に有用な上記本発明を完成するに至った。

本発明における単糖類としては例えばL-アラビノース、D-キシロース、D-リボース、D-グルコース、D-マンノース、D-ガラクトース、D-フルクトース、また二糖類としてはマルトース、セロビオース、トレハロース、ゲンチオビオース、イソマルトース、乳糖、シヨ糖等が挙げられる。

本発明における炭素数6~18の脂肪族炭化水素は直鎖状でも分枝状でもよく、又飽和或いは不飽和のどちらでもよい。

上記飽和炭化水素から水素原子が1つ除かれて生成する飽和炭化水素基としては、例えばヘキシル、ヘプチル、オクチル、ノニル、デシル、ウンデシル、ドデシル、トリデシル、テトラデシル、ヘキサデシル、オクタデシル、2-メチルヘキシル、2-エチルペンチル、2-エチルヘキシル、2-エチルヘプチル、2-エチルオクチル、2-エチルノニル、2-エチルデシル、2-エチルウンデシル、3,7-ジメチルオクチル、2-ヘキシルデシル、2-オクチルデシル、2,4,4-トリメチルペンチル等の直鎖及び分枝鎖のものが挙げられる。又、不飽和炭化水素基としては、例えばCis-3-ヘキセニル、1-エテニルヘキシル、オレイル、リノレイル等が挙げられる。

上記糖類と脂肪族炭化水素とのエーテルもしくはチオエーテル化合物の中でも下記式(1)及び(2)



(1)

(2)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6~18の脂肪族炭化水素基を示す)で表わされる化合物が好ましい。

これらの好ましい化合物の具体例としては以下のものが挙げられる。

n-オクチル-β-D-グルコピラノシド、

2-エチルヘキシル-α,β-D-グルコピラノシド、

n-オクチル-β-D-チオグルコピラノシド、

n-ヘプチル-β-D-チオグルコピラノシド、

n-ラウリル-β-D-マルトピラノシド

これらの糖類の脂肪族炭化水素との(チオ)エーテル類は生体粘膜、例えば直腸粘膜、その他の胃腸管粘膜、膣粘膜、口腔粘膜、経粘膜、鼻粘膜を通しての薬物の吸収性を著しく高め、バイオアベイラビリティーを良好に改善せしめることができる。他方これらの糖類の脂肪族炭化水素との(チオ)エーテル類は生体粘膜刺激性が少なく安全な化合物であり、容易に入手できるものである。

本発明で吸収促進効果を期待される薬物として

は、生体膜透過性が、増強剤を必要とする程度に低い薬物であり、例えば抗炎症剤、循環器官用剤、抗微生物剤、ホルモン剤、制癌剤、抗アレルギー用剤、呼吸器官用剤、中枢神経系用剤、末梢神経系用剤、生物学的製剤等にその例を見い出すことができる。

抗炎症剤としては、例えばアロプリノールが挙げられ、循環器官用剤としては、例えばメチルドパ、グアネチジンの如き抗高血圧剤、トラピジル、クエン酸ニカノテートの如き血管拡張剤、プロプラノロール、コンドロイチン硫酸の如き抗血液凝固剤等を挙げることができる。

抗微生物剤としては、例えばペニシリンG、ペニシリンV、メチシリン、クロキサシリン、アンピシリン、ヘタシリン、シクラシリン、アモキシシリン、カルベニシリン、スルベニシリン等のペニシリン型抗生物質、セファピリン、セファロリジン、セフォキシチン、セファロチン、セファゾリン、セファログリシン、セファレキシン等のセファロスポリン型抗生物質、ストレプトマイシン、カナマイシン、ゲンタマイシン、フラジオマイシン等のアミノグリコシド型抗生物質などが挙げられる。

ホルモン剤としては、例えばインシュリン、アンジオテンシン、バソプレシン、プロチレリン、ゴナドトロピン放出ホルモン、コルチコトロピン、黄体刺激ホルモン、黄体形成ホルモン、カルシトニン、ガストリン等が挙げられる。

制癌剤としては、例えば5－フルオロウラシル、ウラシル、6－メルカプトプリン、メトトレキサート、ブレオマイシン、ダウノルビシン、ドキソルビシン、L－アスパラギナーゼなどが挙げられる。

抗アレルギー用剤、呼吸器官用剤としては、例えばクロモグリケートの如き抗喘息剤などが挙げられる。中枢神経系用剤としては、例えば、臭化水素酸スコポラミン等が挙げられる。末梢神経系用剤としては、例えばプロカイン、メピバカイン、テトラカインなどが挙げられる。生物学的製剤としては、例えばトリプシン、キモトリプシン、ウロキナーゼ、インターフエロン、インターロイキンなどが挙げられる。

上記薬物は本発明に適用できるものの1例であつて全てではないと理解されるべきである。

又、本発明の粘膜吸収促進剤は上記薬剤と同時に又はその前後に投与することができるが、好ましくは予め配合剤としておくのが良い。

本発明の経粘膜吸収促進剤を用いた粘膜投与製剤にあつては、有効成分の配合量は薬物の種類、量、製剤の形態などによつて異なり一概には言えないが、製剤全重量に対して0.1～20重量％が好ましく、より好ましくは0.5～5重量％である。

本発明の経粘膜吸収促進剤を用いた粘膜投与製剤は例えば坐剤、溶液剤、懸濁剤、フイルム剤、エアゾール剤、錠剤、顆粒剤、細粒剤等が挙げられるが、目的とする剤形に応じて、薬物と経粘膜吸収促進剤以外の成分を含有せしめることができる。例えば坐剤とする場合の基剤としては炭素数6～30の脂肪酸とグリセリンのエステル類、例えばダイナミツト・ノーベル社製、ウイテツプゾール、ミグリオール(いずれも商標)、ヤシ油、大豆油等の植物油、又はこれらを水素添加、アセチル化、分画抽出等により改質したもの等が挙げられ、またソフトカプセル坐剤とする場合には剤皮としてゼラチン等が挙げられる。溶液剤とする場合にはエタノール、精製水、グリコール等が通常用いられ、懸濁剤の場合にはアラビアゴム、トラガント、ゼラチン、メチルセルロース、カルボキシメチルセルロース(ＣＭＣ)等が通常用いられる。フイルム剤の場合にはヒドロキシプロピルセルロース、メチルセルロース、ポリビニルピロリドン、ポリビニルアルコール等の基剤が用いられ、錠剤、顆粒剤、細粒剤の場合には乳糖、結晶セルロース、とうもろこしでんぷん等の賦形剤やヒドロキシプロピルセルロース、メチルセルロース等の結合剤等が通常用いられる。又エアゾール剤の場合には噴射剤としてジクロロジフルオロメタン等が通常用いられる。

これらの添加物を含有する粘膜投与製剤は、通常行われている公知の方法によつて製造すること

ができ、その投与量も公知の量で良く、通常成人体重当り1日の有効成分が約0.01～20mg／kgの範囲とするのが好ましい。

(実　施　例)

次に本発明の吸収促進剤を配合した製剤の具体的な処方例を掲げる。

処方例1

セファロリジン	500mg
n－ラウリル－β－D－マルトピラノシド	30mg
ウイテップゾール W－35	1470mg
1坐剤当り	2000mg

上記配合割合で坐剤を調製した。

処方例2

アンピシリンナトリウム	250mg
2－エチルヘキシル－α,β－D－チオグルコピラノシド	40mg
ウイテップゾール W－35	1710mg
1坐剤当り	2000mg

上記配合割合で坐剤を調製した。

処方例3

インシュリン	50 U
n－オクチル－β－D－グルコピラノシド	2mg
精製水	適量
1回噴霧量当り	0.1ml

上記配合割合で経鼻投与(ネブライザー)用の溶液剤を調製した。

処方例4

セファロチンナトリウム	250mg
n－オクチル－β－D－チオグルコピラノシド	100mg
結晶セルロース	150mg
デンプングリコール酸ナトリウム	150mg
ヒドロキシプロピルセルロース	20mg
ヒドロキシプロピルセルロースフタレート	300mg
マクロゴール 6000	30mg
1包当り	1000mg

上記配合割合で腸溶性顆粒剤を調製した。

処方例5

セフピラミド	18重量部
n－ラウリル－β－D－マルトピラノシド	2重量部
ウイテップゾール W－35	80重量部

上記配合割合で坐剤を調製した。

処方例6

セフピラミド	18重量部
n－ラウリル－β－D－マルトピラノシド	1重量部
ウイテップゾール W－35	81重量部

上記配合割合で坐剤を調製した。

処方例7～9

pH7.4のリン酸緩衝食塩水100mlに対し、n－オクチル－β－D－グルコピラノシド(n－OG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)、20mM(約0.6W/V%)の濃度に調製して溶液剤とした。

処方例10～12

処方例7と同様にしてn－オクチル－β－D－チオグルコピラノシド(OTG)をそれぞれ100mM(約3.1W/V%)、50mM(約1.5W/V%)、10mM(約0.3W/V%)の濃度に調製して溶液剤とした。

処方例13～14

処方例7と同様にしてn－ヘプチル－β－D－チオグルコピラノシド(HTG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)の濃度に調製して溶液剤とした。

処方例15～17

処方例7と同様にして2－エチルヘキシル－α,β－D－グルコピラノシド(b－OG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)、35mM(約1.0W/V%)の濃度に調製して溶液剤とした。

処方例18～21

処方例7と同様にしてn－ラウリル－β－D－マルトピラノシド(LM)をそれぞれ50mM(約2.6W/V%)、10mM(約0.5W/V%)、5mM(約0.26W/V%)、2.5mM(約0.13W/V%)の濃度に調製して溶液剤とした。

処方例22

セフピラミド　18重量部
n－ヘキシル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例23
セフピラミド　18重量部
n－ヘキシル－β－D－チオグルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例24
セフピラミド　18重量部
n－オクタデシル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例25
セフピラミド　18重量部
1－エテニルヘキシル－α－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例26
セフピラミド　18重量部
9－オクタデセニル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

次に吸収試験を示し、経粘膜吸収促進作用を説明する。

＜吸収試験＞

当試験においては、Wistar系雄性ラット(240～300g)の結腸下部より肛門部までの6cmを吸収部位として行った。

(1) 処方例7～21の溶液剤及び対照例としてpH 7.4のリン酸塩緩衝食塩水100mlに難吸収性の薬物モデルとして水溶性の蛍光色素である6－カルボキシフルオレセイン(CF)0.1gを溶解し、16時間絶食したペントバルビタール麻酔下のラットの大腸ループ内に体重250g当り125μl投与後、頸動脈より経時的に採血を行い、血中6－カルボキシフルオレセイン濃度を蛍光光度法(EX：490nm、EM：520nm)により定量した。結果を第1～5図に示す。

(2) 処方例7(n－OG、約2.9W/V%)、処方例10(OTG、約3.1W/V%)の溶液剤及び対照例としてpH 7.4のリン酸塩緩衝食塩水100mlにセフピラミド12g又はペプレオマイシン1.6gを各々溶解し、16時間絶食したペントバルビタール麻酔下のラットの大腸ループ内に上記の各溶液を体重250g当り125μl投与後、頸動脈より経時的に採血を行い、血中セフピラミド又はペプレオマイシン濃度をペーパーディスク法(bacillus sub. ATCC6623)により定量し、それぞれの血中濃度下面積(AUC)を求めた。結果を第1表に示す。

第1表

薬物	粘膜吸収促進剤	最高血中濃度 (μg/ml)	$AUC^{0-2.5h}$ (μg・min/ml)
セフピラミド (60mg/kg)	－	－	223.6± 35.7
	n－OG 100mM	51.6±12.0	2594.9±225.9
	OTG 100mM	45.3± 5.7	2692.0±189.3
ペプレオマイシン (8mg/kg)	－	－	50.8± 11.3
	n－OG 100mM	3.6± 0.4	233.3± 16.3
	OTG 100mM	4.9± 0.8	361.2± 25.1

(3) 処方例5、6及び対照例としてセフピラミド18重量部、ウイテップゾール W－35(82重量部)の配合割合より成る処方を固化、成形した坐剤83mgを16時間絶食したラットの直腸に投与し、以下吸収実験(2)と同様に採血及び血中濃度の定量を行った。結果を第6図に示す。

以上の吸収試験から本発明の経粘膜吸収促進剤は難吸収性薬物の粘膜吸収に優れた効果を有することが明らかである。

4．図面の簡単な説明

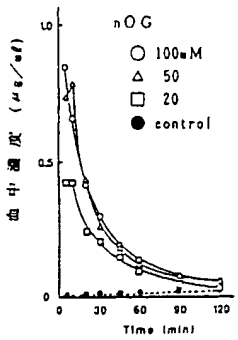
第1～6図は吸収試験における薬物の血中濃度の経時変化を示すグラフである。

（以　上）

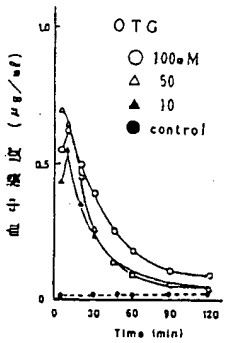
出　願　人　　大鵬薬品工業株式会社

代　理　人　　弁理士　田　村　　巌

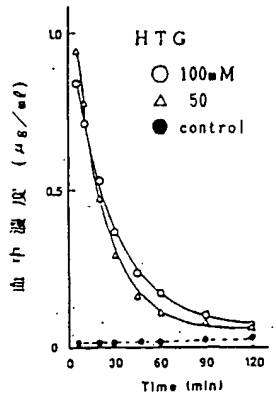
第 1 図



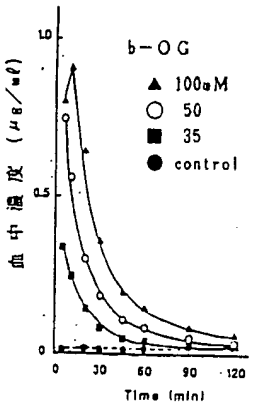
第 2 図



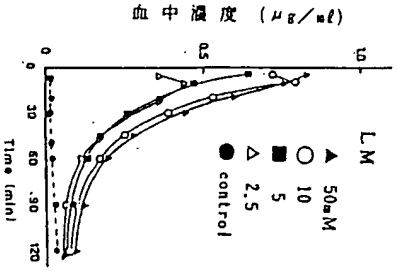
第 3 図



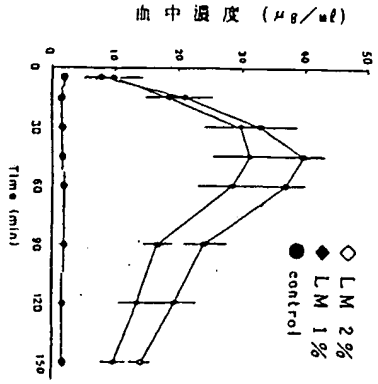
第 4 図



第 5 図



第 6 図



OIPE IAP52
JUL 25 2006
PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. § 1.97, enclosed are references relating to the above-identified application. For the convenience of the Examiner, the reference is listed on the attached Form PTO-1449. As all cited documents are U.S. references, no hard copies are enclosed herewith.

It is respectfully requested that these references be considered in the examination of this application and their consideration be made of written record in the application file.

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Karen LePari

Karen LePari

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356894-12

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Respectfully submitted,

Date: July 21, 2006

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OIPE IAP52 JUL 25 2006 PATENT & TRADEMARK OFFICE

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1. Information Disclosure Statement (2 pgs.);
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FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1636

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JUL 25 2006
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U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA	6,524,557 B1	02/25/2003	Backstrom et al.			
	AB	2003/0100755 A1	05/29/2003	Sham et al.			
	AC	2003/0118594 A1	06/26/2003	Nag et al.			
	AD	2004/0115135 A1	06/17/2004	Quay			
	AE	2004/0126358 A1	07/01/2004	Warne et al.			
	AF	2004/0147473 A1	07/29/2004	Warrell, Jr.			
	AG	2005/0234101 A1	10/20/2005	Stenkamp et al.			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

EXAMINER	DATE CONSIDERED

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Form 1449

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IAP18
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PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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2. PTO Form 1449 (1 pg.);
3. References (4); and
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Karen LePari

Karen LePari

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356897-183

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Respectfully submitted,

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PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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INFORMATION DISCLOSURE STATEMENT

Sir:

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Karen LePari

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356897-183

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Docket No. AEGIS1210	Serial No.: 11/127,786
	Applicant: Meezan et al.	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date: May 11, 2005	Group Art Unit: 1636

OIPE IAP18 NOV 0 2 2005 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA	5,661,130	08/26/1997	Meezan and Pillion			

FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

	AB	Hovgaard, Lars et al., "Stabilization of insulin by alkylmaltosides. A. Spectroscopic evaluation", *International Journal of Pharmaceutics*, **Vol. 132, 107-113**, 1996
	AC	Hovgaard, Lars et al., "Stabilization of insulin by alkylmaltosides. B. Oral absorption in vivo in rats", *International Journal of Pharmaceutics,* **Vol 132, 115-121,** 1996
	AD	Tsuchido, Tetsuaki et al., "Lysis of Bacillus subtilis Cells by Glycerol and Sucrose Esters of Fatty Acids", *Applied and Environmental Microbiology,* **Vol. 53, No. 3, 505-508**, 1987
	AE	Watanabe, Takashi et al., "Antibacterial Carbohydrate Monoesters Suppressing Cell Growth of Streptoccus mutans in the Presence of Sucrose", *Current Microbiology,* **Vol. 41, 210-213,** 2000

EXAMINER	DATE CONSIDERED
GT\6465702.1 356897-183	

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Form 1449 1

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International Journal of Pharmaceutics 132 (1996) 107–113

international journal of pharmaceutics

Stabilization of insulin by alkylmaltosides. A. Spectroscopic evaluation

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Abstract

The aggregational behavior of native bovine insulin has been studied by circular dichroism and quasi elastic laser light scattering. The influence of a homologous series of alkylmaltosides on the self-association and aggregation of insulin was investigated. Significant stabilization of insulin was observed for the alkylmaltosides. Circular dichroism revealed that dodecylmaltoside was the most promising compound from a stabilizer stand point. Using dodecylmaltoside as the model compound, it was found that micelles were formed in the concentration range of the experiments and micell formation appeared to be important for the stabilization of insulin. Moreover, the results may suggest that insulin partitions into the micelles in an equimolar fashion and that insulin in this 'mixed micellar' form is relatively stable.

Keywords: Insulin; Peptide; Self-association; Aggregation; Laser light scattering; Alkylmaltosides

1. Introduction

Insulin is a polypeptide with a molecular weight of 5733 g/mole (bovine) consisting of 51 amino acids shared between two intramolecular chains. Insulin's conformational structure is well described (Marshall et al., 1971; Blundell et al., 1972; Pullen et al., 1976; Arquilla et al., 1978; De Meyts et al., 1978; Baker et al., 1988). The self-association and aggregational behavior of insulin has also been studied extensively because of the use of the drug in subcutaneous formulations for the treatment of diabetes (Brange, 1994).

The region on the insulin molecule responsible for aggregational behavior has been identified as a hydrophobic segment near the B-chain terminus (De Meyts et al., 1978; Baker et al., 1988). By exchanging amino acids in this border region, analogs with lower association tendencies were obtained (Brange et al., 1988). The association state of insulin at neutral pH in aqueous solution is predominantly hexamer (Hvidt, 1991). Removal of the region responsible for aggregation was

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shown to reduce association (Goldman and Carpenter, 1974). The fibrillation is a major problem for long-term storage and pump systems, and may affect the level of side effects encountered by diabetic patients in exogenous insulin treatment (Brange, 1987). It has been shown that aggregation of insulin in containers not only could be caused by denaturation at the solution/container interface but also by the constantly changing solution/air interface (Schrader and Pfeiffer, 1985). Moreover, as the temperature of a system is elevated, the aggregation increases dramatically.

Insulin association and aggregation has been studied by both circular dichroism and laser light scattering (Sato et al., 1983; Martindale et al., 1982; Bohidar and Geissler, 1984; Sluzky et al., 1991; Hvidt, 1991). Moreover, it is well known that micellar systems solubilize proteins. Insulin has been stabilized in such systems by many amphiphiles. Aggregation has most often been determined in an indirect manner as solution turbidity depression (Lougheed et al., 1983; Grau, 1985; Brange, 1987). Polypropylene glycol (PPG)/polyethylene glycol (PEG) block copolymer has been shown very effective in reducing the extent of aggregation (Thurow and Geisen, 1984; Chawla et al., 1985).

Alkylmaltosides were previously shown to stabilize insulin in solution against aggregation (Hovgaard, 1991; Hovgaard et al., 1992). The purpose of this present study was to verify the stabilization of insulin by dodecylmaltoside (DDM). Therefore, circular dichroism and quasi elastic laser light scattering was employed. Based on the characterization of DDM and DDM-insulin complexes, a model for stabilization has been proposed.

2. Materials and methods

2.1. Synthesis of alkylmaltosides

The synthesis of the alkylmaltosides has been described elsewhere (Hovgaard, 1991). Briefly, peracetylated bromomaltose was allowed to react with the fatty alcohols under anhydrous conditions. The protective acetyl groups were then hydrolyzed under alkaline conditions and the crude product was isolated. The products (octylmaltoside (OM), decylmaltoside (DM), dodecylmaltoside (DDM), tetradecylmaltoside (TDM), hexadecylmaltoside (HDM), and octadecylmaltoside (DDM) were isolated and purified by diethyl-ether precipitation followed by preparative flash-chromatography. The yields varied from 7 to 42% and the purities were above 99%, as determined by elemental analysis.

2.2. Insulin stability measured by circular dichroism

The stability of insulin in solution was studied under agitation. Bovine insulin (Sigma Chemical Co., St. Louis, MO) in a concentration of 0.1 mg/ml in 0.1 M phosphate buffered saline (PBS) of pH 8.0 was mixed with each of the maltosides in concentrations ranging from 0.2 mmole/ml (0.1 mg/ml) to 12.6 mmole/ml (6.4 mg/ml), equivalent to insulin: alkyl maltoside molar ratios of 1:11 to 1:720. Gentamycin (Sigma) was added in a concentration of 0.0025% to prevent bacterial growth. Agitation took place in a shaking water bath (37.0 $\pm$ 0.1°C) at a rate of 100 $\pm$ 1 strokes/min, 35 mm/stroke. Aggregation was followed by circular dichroic spectral analysis of insulin at 209 nm on a JASCO J-40A (Automatic Recording Circular Dichroism Spectropolarimeter, Japan) (Hovgaard et al., 1992).

2.3. Determination of critical micelle concentration (CMC)

CMC was determined by laser light scattering. Particle free borosilicate glass test tubes (7.5 x 100 mm) were used for all measurements. A series of concentrations for each maltoside was prepared in 0.1 M PBS of pH 8.0. The samples were filtered through a 0.2 μm Gelman Acrodisc syringe filter and sealed with a dust-free plastic stopper. The tube was placed in the sample holder of the laser light scattering goniometer (Brookhaven Instruments Corporation, Holtsville, N.Y.). The laser was equipped with a green Argon-ion laser with a power range of 10 mW–2 W and adjustable wavelength (4 880 and 5 145 Å). The laser appara-

tus has been described elsewhere (Cohen et al., 1990). The laser power was adjusted to 500 mW. All experiments were performed at a scattering angle of 90°. The scattering intensity and the size of micelles were measured as functions of concentration. All experiments were done in triplicate at room temperature (21°C).

2.4. Insulin stability measured by laser light scattering

Insulin was investigated in a concentration of 175 μM (1.0 mg/ml) in 0.1 M phosphate buffer of pH 8.0. Based on the CD results, DDM was chosen for this part of the study. Dodecylmaltoside was added in concentrations below and above CMC. The molar ratios of insulin to dodecylmaltoside studied were 1:0.6, 1:2.3, 1:11 and 1:45. Samples were prepared fresh less than 1 h prior to the start of experiments. The light scattering intensity of the solutions were measured daily. To study the pH dependent self-association, a series of 0.05 M phosphate buffers (pH 2.0–12.0) were prepared. Insulin was dissolved in the different buffers in a concentration of 1.0 mg/ml in order to minimize data collection time. Light scattering intensity and diffusion constants of these solutions were measured immediately.

2.5. Data analysis

CMC was determined from plots of scattering intensity versus concentration. The scattered light intensity is analyzed through an autocorrelation function (Cohen et al., 1990)

$$R(t) = \sum_t I_s(t) I_s(t + \tau) \quad (1)$$

where $I_s(t)$ is the intensity at a specific time and $I_s(t + \tau)$ at a later time, τ. In polydisperse systems, the autocorrelation function contains a sum of exponentials (Mazer, 1985)

$$R(t) = \left(\sum_i G_i e^{-D_i Q^2} \right)^2 \quad (2)$$

where G_i is the relative intensity scattered, D_i is, in the case of a polydisperse population, an average diffusional coefficient of the ith particle and q is the size of the scattering vector. Assuming that the particles are spherical, the hydrodynamic radius (R_h) can be computed through the Stokes-Einstein equation (Mazer et al., 1976)

$$R_h = \frac{k_B T}{6\pi\eta D} \quad (3)$$

Insulin self-association can be studied by QELS with great advantages (Bohidar and Geissler, 1984; Hvidt, 1991; Sluzky et al., 1991). For molecular weight determinations, the ratio of scattered to incident light, corrected for geometric factors such as the detection angle of scattered light, is expressed by the Rayleigh ratio R_θ (Eisenberg and Crothers, 1979)

$$R_\theta = \frac{4\pi^2 n_o^2 \left(\frac{\partial n}{\partial c}\right)^2}{N_A \lambda^4} c M_w \quad (4)$$

where n_o is the solvent refractive index, N_A is Avogadro's number, M_w is the molecular weight, λ is the wavelength of the incident light and c the concentration of solute. Based on literature values for the concentration dependencies of refractive indexes for insulin and surfactant solutions, we have made the assumption that they can be equated (Mysels and Princen, 1959; Rosen, 1989; Hvidt, 1991). Based on the scattering data for insulin solutions, it is reasonable to assume that the predominant species of insulin in neutral solutions is the hexamer (Brange, 1994). A close examination of equation 4 then reveals the following simple relationship

$$R_\theta = K_c M_w \quad (5)$$

in which K is a constant representing the bracketed expression in equation 4. From equation 5, the molecular weight of the scattering species can then easily be estimated.

3. Results and discussion

3.1. Insulin stability measured by circular dichroism

At pH 8.0 the circular dichroic spectrum of insulin possesses a significant negative trough at

220 nm and 209 nm, corresponding to insulin's specific tertiary structure. As insulin aggregates, this structure gradually changes. Since the negative trough at 209 nm has the strongest spectral activity, this wavelength was followed. In this experimental series, the molar ellipticity was found to range from -7.5×10^3 to -8.5×10^3 deg cm^2/dmole. This was not changed by the presence of any of the stabilizers. The first sign of aggregation could be registered as changes in the CD spectrum, followed by visual opaqueness. The results are given in Fig. 1. The highest stabilization was observed for DM (1:64 (w/w)) and DDM (1:4 (w/w)). After 57 d, the DDM-insulin complex was found to be stable and to possess full biological activity after i.v. injection in rats as determined by blood glucose levels. These results suggest that the effect of the alkylmaltosides is governed by their length and complex ratio to insulin. Moreover, the stabilization was found to correlate with the CMC. This will be touched upon later.

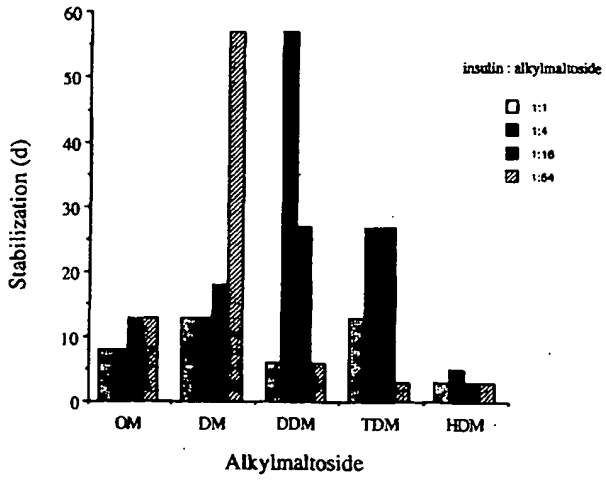


Fig. 1. Time of insulin stabilization by the stabilizers: OM, DM, DDM, TDM, HDM and ODM in the w/w ratios 1:1, 1:4, 1:16 and 1:64 (insulin to stabilizer) equivalent to molar ratios of 1:11, 1:45, 1:180 and 1:720 in the case of DDM. Time of insulin stabilization is determined to be at the time of 90% preservation of initial ellipticity (day 1) in the circular dichroic spectrum of insulin.

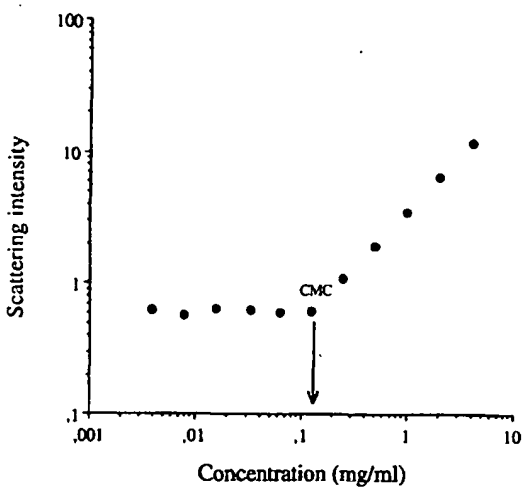


Fig. 2. Laser light scattering intensity as a function of concentration of dodecylmaltoside. The critical micelle concentration (CMC) is observed at the break on the curve.

3.2. Determination of critical micelle concentration

The critical micelle concentration was found at the point of discontinuity in the plots of scattering intensity versus concentration, as shown for dodecylmaltoside in Fig. 2. The plot allows for a precise determination of the event. All of the alkylmaltosides showed micelle formation, with Table 1 listing the CMC values. The shorter chain maltosides (octyl to dodecyl) show CMC of 5–0.24 mM, along with a micellar size of about 33 Å. This correlates with values reported for alkylglucosides by Rosen (1989). It was reported that octyl- to dodecyl- glucoside, which have smaller polar head groups, but the same alkyl chain

Table 1
Critical micelle concentration of alkylmaltosides

Compound	Critical micelle concentration	
	[mg/ml]	[mM]
Octylmaltoside	2.3	5.07
Decylmaltoside	0.80	1.66
Dodecylmaltoside	0.12	0.24
Tetradecylmaltoside	0.075	0.13
Hexadecylmaltoside	0.0081	0.014
Octadecylmaltoside	0.0017	0.0029

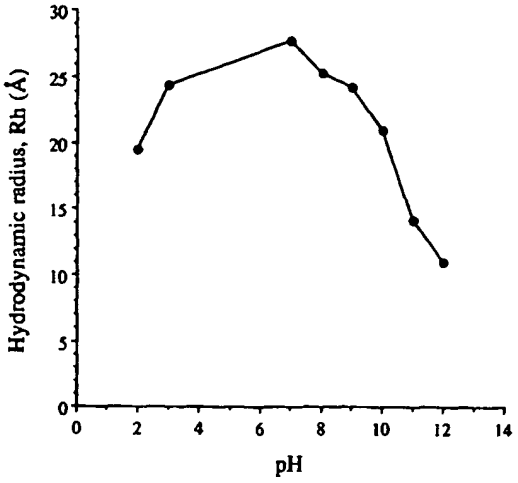


Fig. 3. Insulin aggregational pattern over a pH range from 2 to 12. Hydrodynamic radii of insulin as a function of pH in the solution measured by dynamic laser light scattering.

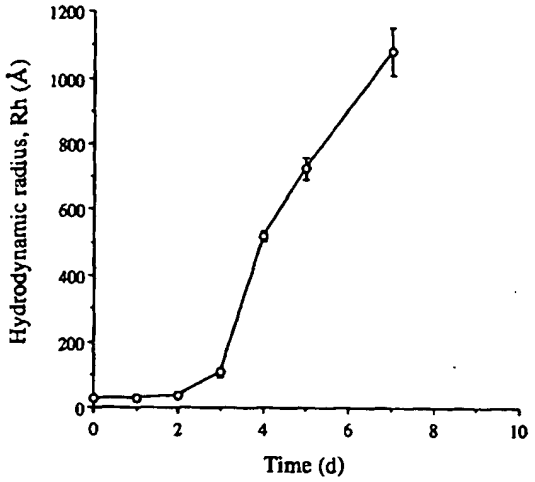


Fig. 4. Hydrodynamic radius of insulin, 1 mg/ml in 0.1 M PBS (pH 8.0), as a function of time measured by dynamic laser light scattering.

lengths, had CMCs from 25 mM to 0.19 mM (Rosen, 1989). Moreover, the hydrodynamic radii for micelles are in the range of 25–150 Å for an ionic amphiphile compound like sodium dodecyl sulfate (Mazer, 1985). The solubility of the maltosides up to tetradecylmaltoside was not reached within the concentration range of the experiment. However, longer chain analogs were less soluble and showed some turbidity at the high concentrations. The sizes of the micelles increased slightly with increasing length of the alkyl chain. An initial 'plateau' at a size of 33 Å for OM, DM and DDM could be caused by the bulky nature of the maltose head group on the shorter chain alcohols. The micellar sizes of the largest maltosides were not determined.

3.3. Insulin stability measured by laser light scattering

The association state of insulin was determined at pH from 2 to 12. The insulin solutions showed predominantly dimers at low pH and monomer at high pH, with radii of 19 and 11 Å, respectively (Fig. 3). These results are in full agreement with observations by Bohidar and Geissler (1984), who found R_h for monomer insulin to be 12–13 Å. At neutral pH, the associational state was hexamer, showing a size of 28 Å which was in accordance with other reports (Brange, 1994). The aggregation was followed in neutral solutions of insulin. Fig. 4 shows the change in the hydrodynamic radius with time. The radius increased from 27 Å at time zero to over 1000 Å after just 1 week. The increase in the hydrodynamic radius suggests macromolecular aggregation. When dodecylmaltoside was added, insulin did not aggregate as readily (Fig. 5). The hydrodynamic radius is plot-

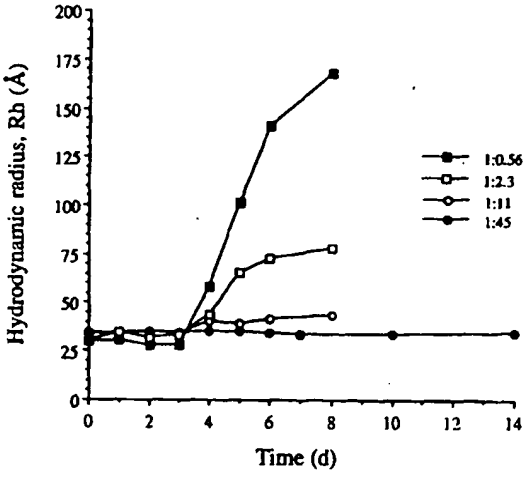


Fig. 5. Hydrodynamic radius of insulin, 1 mg/ml in 0.1 M PBS (pH 8.0), containing dodecylmaltoside in various molar ratios, as a function of time measured by dynamic laser light scattering.

Table 2
QELS data for pure insulin and DDM solutions

	R_h (Å)	I_{ins}/I_t	C (mg/ml)
Insulin	28	0.7	1
Dodecylmaltoside	35	3.2	4

ted as a function of time for all the tested concentrations of dodecylmaltoside. Samples containing insulin and maltosides showed an initial hydrodynamic radii ranging from 27 to 33 Å, depending on the concentration of dodecylmaltoside. The solutions tested ranged from 98 x 10^{-3} to 7.8 mM dodecylmaltoside. As the concentrations of dodecylmaltoside were raised, higher stabilization was observed.

The theoretical description of the insulin dodecylmaltoside complex composition is not easy. In this study, we will try to discuss the possible ways of stabilization. QELS measurements on the pure components gave the values given in Table 2. Insulin in a concentration of 1 mg/ml can be assumed to represent insulin hexamer solution characteristics. Therefore, the molecular weight of the scattering species is 34 400 g/mole. Equation 6 states that toluene normalized scattering intensity of a mixture of solutes with different molecular weights is proportional to the sum of the product of concentration, c, and molecular weight, M (Mazer et al., 1976)

$$\frac{I_i}{I_t} = K\sum_i c_i M_i \quad (6)$$

If equation 6 is used on the pure insulin solution, the constant K can be determined.

$$\frac{I_{ins}}{I_t} = K_c M_w \Rightarrow K = \frac{0.7}{1 \cdot 34400} = 2 \times 10^{-5}$$

K can be used as a good approximation for the calculation of the molecular weight of a micelle. From the results for pure dodecylmaltoside solution

$$M_w = \frac{3.3}{4 \cdot 2 \times 10^{-5}} = 41000$$

This suggests that the aggregation number of DDM in a micelle is approximately 80. Based on this knowledge, Table 3 has been constructed. The stabilization measured by CD under agitation and QELS without agitation suggests that DDM is stabilizing insulin in solution. In the case of agitation, an optimum stabilization was reached when 0.6–2.3 mole of micelles were present per mole of insulin hexamer. This indicates that an interaction of the insulin molecule with micelles of DDM is essential for the stabilization. However, if 9 moles of DDM micelles were present, destabilization was observed. This could be due to denaturation of the insulin molecule. The maximum stabilizing concentration of micelles was confirmed by QELS where the initial hydrodynamic radius of the mixture of insulin and dodecylmaltoside micelles was preserved for at least 2 weeks.

In conclusion, alkylmaltosides were shown to have a great potential as stabilizers for insulin. The concentration range for stabilization determined by circular dichroism correlated with the CMC values for DM and DDM. It was not possible to show this for other maltosides. DDM may stabilize insulin in a mixed micellar fashion. At this point, only speculation can be made on how the stabilization of insulin by DDM micelles takes place. The micelles may pose as an attractive phase for the insulin dimer or monomer. Therefore, these species can advantageously partition into the micelles instead of taking part in aggregation of insulin in higher states. This will have to be studied in the future. However, if this hypothesis is true, the reduction in molecular weight of the insulin form presented to the mucosal surface can be reduced and a higher transport expected.

Table 3
Various molar ratios of insulin to DDM calculated on basis of QELS

Insulin:DDM (w/w)	Insulin:DDM (mol/mol)	Insulin:micelles (mol/mol)
1:0.05	1:0.56	1:0.007
1:0.2	1:2.3	1:0.028
1:1	1:11	1:0.14
1:4	1:45	1:0.6
1:16	1:180	1:2.3
1:64	1:720	1:9

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Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
Filed:	May 11, 2005	Conf. No.:	5393
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

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Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **150** *to complete the basic filing fee for a small entity.*
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$5150** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

08/15/2005 MAHMED1 00000092 11127786

01 FC:2011	150.00 OP
02 FC:2111	250.00 OP
03 FC:2311	100.00 OP
04 FC:2051	65.00 OP
05 FC:2202	650.00 OP

Total additional fee(s) required for this application is **$5715** for a Small Entity

- **$150** Statutory basic filing fee.
- **$65** Late oath or declaration Surcharge.

- The application search fee has not been paid. Applicant must submit **$250** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit **$100** to complete the examination fee for a small entity in compliance with 37 CFR 1.27

- Total additional claim fee(s) for this application is **$5150**
  - **$2200** for **22** independent claims over 3.
  - **$2950** for **118** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
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Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

OIPE
AUG 12 2005
PATENT & TRADEMARK OFFICE

PATENT
Attorney Docket No.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Serial No.	11/127,786	Examiner:	Not Yet Assigned
Filing Date	May 11, 2005		
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

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P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

In connection with the above-identified Patent Application, entry of the amendment is respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 4 of the paper.

Remarks begin on page 11 of this paper.

CERTIFICATION UNDER 37 CFR §1.8
I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on this date, **August 10, 2005,** in an envelope addressed to: Mail Stop AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Aldon Griffis *(Name of Person Mailing Paper)*
Aldon Griffis **August 10, 2005** *(Signature)* *(Date)*

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356894-12

I. AMENDMENTS

A. In the Specification

Please amend the following paragraphs:

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25%TDM and IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following ~~oral administration~~ intraperitoneal (i.p.) injection of glucose (i.e., in a so-called "glucose tolerance test").

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a ~~hydrophobic~~ hydrophilic saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or ~~branching~~ length of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast

to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

Please amend Table I, on page 44, as shown below:

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	[[144]] 141 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

B. In the Claims

Please cancel claims 47 to 138 without prejudice. Upon entry of the present amendment, the status of the claims will be as follows:

1. (Original) A surfactant composition comprising of at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed with a drug, the surfactant stabilizes the biological activity and increases the bioavailability, of the drug.

2. (Original) The composition of claim 1, wherein the drug is a peptide or a protein.

3. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than the daily intake amount of the surfactant.

5. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than the daily intake amount of the surfactant.

6. (Original) The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 1000 times higher than the daily intake amount of the surfactant.

7. (Original) The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. (Original) The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. (Original) The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. (Original) The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. (Original) The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system.

13. (Original) The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. (Original) The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 20%.

15. (Original) The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 5%.

16. (Original) The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 2%.

17. (Original) A therapeutic composition comprising of at least one biologically active compound(s) and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside and/or saccharide alkyl ester and wherein said composition stabilizes the biological activity of the drug, for at least about 6 months from about 4°C to 25°C.

18. (Original) The composition of claim 17, wherein the pH of the composition is less than 8.0.

19. (Original) The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. (Original) The composition of claim 17, wherein the composition concentration is from about 0.01% to 20%.

21. (Original) The composition of claim 17, wherein the composition concentration is from about 0.01% to 5%.

22. (Original) The composition of claim 17, wherein the composition concentration is from about 0.01% to 2%.

23. (Original) A stable therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. (Original) A stable therapeutic composition according to claim 17, wherein the administration to the subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of said biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of said subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to said subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. (Original) The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. (Original) The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to the subject.

27. (Original) The therapeutic composition of claim 17, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active compound(s) in said CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater compared to an AUC of said biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to said subject.

28. (Original) The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields an area under concentration curve (AUC) of said biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. (Original) The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. (Original) The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. (Original) A method of administering a drug composition comprising of a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

32. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than the daily intake amount of the surfactant.

34. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than the daily intake amount of the surfactant.

35. (Original) The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than the daily intake amount of the surfactant.

36. (Original) The method of claim 31, wherein the surfactant reduces the bioavailability variance from patient to patient.

37. (Original) The method of claim 31, wherein the composition does not enter the hepatic portal blood system.

38. (Original) The method of claim 31, wherein the pH of the composition is less than 8.0.

39. (Original) The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. (Original) The method of claim 31, wherein the composition concentration is from about 0.01% to 20%.

41. (Original) The method of claim 31, wherein the composition concentration is from about 0.01% to 5%.

42. (Original) The method of claim 31, wherein the composition concentration is from about 0.01% to 2%.

43. (Original) The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. (Original) The method of claim 1, wherein the composition is further comprised of an enteric coating.

45. (Original) The method of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM).

46. (Original) The method of claim 45, wherein the TDM has anti-bacterial activity.

47 to 138. (Cancelled).

II. REMARKS

The amendments to the specification merely correct typographical errors, and therefore they do not add new matter. For example, in Table I, which was copied from U.S. Patent No. 5,661,130 (which was incorporated in its entirety in the above-identified application), the value for the 90 minute time point should correctly be "141" and not "144."

Upon entry of the present amendment, claims 1 to 46 will be pending.

Claims 47 to 138 are cancelled herein without disclaimer, and without prejudice to Applicants' pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application. There are no new claims. Accordingly, entry of the amendments is respectfully requested.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application. The Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

Reg. No. 45,517

Date: August 10, 2005

for Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO Customer Number 28213
DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

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356894-12

OIPE JC12 AUG 12 2005

ATTORNEY DOCKET NO.:
AEGIS1210

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION**, the specification of which

_____ is attached hereto.

__X__ was filed on May 11, 2005, (Attorney Docket No.: **AEGIS1210**) as U.S. Application Serial No. 11/127,786 and was amended on _____ if applicable (the "Application").

I hereby authorize and request insertion of the application serial number of the Application when officially known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, Code of Federal Regulations ("C.F.R."), § 1.56.

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/649,958	February 3, 2005
(Application Serial No.)	(Filing Date)
60/637,284	December 17, 2004
(Application Serial No.)	(Filing Date)
60/632,038	November 30, 2004
(Application Serial No.)	(Filing Date)
60/609,890	September 14, 2004
(Application Serial No.)	(Filing Date)
60/604,296	August 25, 2004
(Application Serial No.)	(Filing Date)

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of the application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of the Application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Elias Meezan**

Inventor's signature: Elias Meezan

Date: 25 May 2005

Residence: Birmingham, Alabama

Country of Citizenship: USA

Post Office Address: 1202 Cheval Lane
Birmingham, AL 35216

Full name of second inventor: **Dennis J. Pillion**

Inventor's signature: Dennis J. Pillion

Date: 25 May 2005

Residence: Hoover, Alabama

Country of Citizenship: USA

Post Office Address: 1100 Regent Drive
Hoover, AL 35226-3020

Full name of third inventor: **Edward T. Maggio**

Inventor's signature: Edward T. Maggio

Date: 13 May 2005

Residence: San Diego, California

Country of Citizenship: USA

Post Office Address: 18775 Bernardo Trails Drive
San Diego, CA 92128



PATENT
ATTORNEY DOCKET NO.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
File Date:	May 11, 2005		
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY BY ASSIGNEE

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of **USPTO Customer No. 28213** to prosecute the Application for the assignee and transact all business in the United States Patent and Trademark Office connected therewith:

DAVID L. ALBERTI	Registration No. 43,465
DARYL BASHAM	Registration No. 45,869
MARK L. BERRIER	Registration No. 35,066
LISA A. HAILE	Registration No. 38,347
JON IKEGAMI	Registration No. 51,115
PETER R. LEAL	Registration No. 24,226
ALAN A. LIMBACH	Registration No. 39,749
GEORGE C. LIMBACH	Registration No. 19,305
TIMOTHY W. LOHSE	Registration No. 35,255
ANTONY M. NOVOM	Registration No. 45,517
VICTOR REPKIN	Registration No. 45,039
MICHAEL T. ROSATO	Registration No. 52,182
GERALD T. SEKIMURA	Registration No. 30,103
ANDREW V. SMITH	Registration No. 43,132
KIEUN J. SUNG	Registration No. 48,639
EDWARD B. WELLER	Registration No. 37,468
RONALD L. YIN	Registration No. 27,607

GT\6446087.1
356894-12

I hereby authorize and request insertion of the application number of the Application when officially known.

Direct all telephone calls to:

LISA A. HAILE, J.D., PH.D.
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

Address all correspondence to:

LISA A. HAILE, J.D., PH.D.
DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

THE UAB RESEARCH FOUNDATION

By : _____
(Signature)

Name : William S. White
(Typed or Printed Name)

Title : CFO

Date : July 27, 2005

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356894-12

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AUG 12 2005
PATENT & TRADEMARK OFFICE

PATENT
ATTORNEY DOCKET NO.: AEGIS1210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Meezan et al.	Art Unit:	1636
Application No.:	11/127,786	Examiner:	Not Yet Assigned
File Date:	May 11, 2005		
Title:	ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION		

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Alexandria, VA 22313-1450

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ANTONY M. NOVOM	Registration No. 45,517
VICTOR REPKIN	Registration No. 45,039
MICHAEL T. ROSATO	Registration No. 52,182
GERALD T. SEKIMURA	Registration No. 30,103
TAMARA SHIELDS SAMPSELL	Registration No. 52,221
ANDREW V. SMITH	Registration No. 43,132
KIEUN J. SUNG	Registration No. 48,639
EDWARD B. WELLER	Registration No. 37,468
RONALD L. YIN	Registration No. 27,607

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356894-12

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Direct all telephone calls to:

LISA A. HAILE, J.D., PH.D.
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

Address all correspondence to:

LISA A. HAILE, J.D., PH.D.
DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

AEGIS THERAPEUTICS LLC

By : _____
(Signature)

Name : Edward T. Maggio
(Typed or Printed Name)

Title : President and CEO

Date : 5/13/05

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/127,786	05/11/2005	Elias Meezan	AEGIS1210

CONFIRMATION NO. 5393

28213
DLA PIPER RUDNICK GRAY CARY US, LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

FORMALITIES LETTER

OC000000016248993

Date Mailed: 06/10/2005

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **150** *to complete the basic filing fee for a small entity.*
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$5150** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$5715** for a Small Entity

- **$150** Statutory basic filing fee.
- **$65** Late oath or declaration Surcharge.

- The application search fee has not been paid. Applicant must submit **$250** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit **$100** to complete the examination fee for a small entity in compliance with 37 CFR 1.27

- Total additional claim fee(s) for this application is **$5150**
  - **$2200** for **22** independent claims over 3.
  - **$2950** for **118** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
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A copy of this notice MUST be returned with the reply.

Roberta Lucy

Office of Initial Patent Examination (703) 308-1202

PART 3 - OFFICE COPY

22783 U.S. PTO
051105

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112921 U.S.PTO
11/127786
051105

May 11, 2005

ATTORNEY DOCKET NO.: AEGIS1210

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Presented for filing is a new **Provisional-to-Utility** patent application of:

APPLICANTS : Elias Meezan, Dennis J. Pillion and Edward T. Maggio

TITLE : ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

Enclosed are the following papers, including all those required to receive a filing date under 37 CFR § 1.53(b):

Pages of Cover Sheet	1
Pages of Specification	51
Pages of Claims	20
Pages of Abstract	1
Pages of Declaration (Unsigned)	4
Sheets of Drawing (Formal)	3

CERTIFICATION UNDER 37 CFR §1.10
"EXPRESS MAIL" Mailing Label Number: **EV 627 502 002 US**
Date of Deposit: **May 11, 2005**

I hereby certify that this correspondence is being deposited with the United States Postal Service as **"Express Mail Post Office to Addressee"** with sufficient postage on the date indicated above and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

TRUDY GEROVSKE
(Name of Person Mailing Paper)

Trudy Gerovske May 11, 2005
(Signature) *(Date)*

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356894-12

This request includes Three (3) sheets and the following:

- Application Data Sheet (3 pages); and
- Return Receipt Postcard.

This application is a **Provisional-to-Utility** application and claims the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now pending; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now pending. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

Applicants claim **SMALL ENTITY** status in the above-identified application.

The filing fee is calculated as follows:

	Number Filed		Number Extra		Rate			Fee	
					Small Entity	Large Entity		Small Entity	Large Entity
Total Claims	193-20	=	173	X	$25	$50	=	$4,325.00	$ .00
Independent Claims	23-3	=	20	X	$100	$200	=	$2,000.00	$ .00
Multiple Dependent Claims Present: __x__ Yes ____ No					$180	$360		$ 180.00	N/A
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If this application is found to be INCOMPLETE, or if a telephone conference would otherwise be helpful, please call the undersigned at (858) 677-1456.

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A duplicate copy of this transmittal letter is enclosed. Kindly acknowledge receipt of this application by returning the enclosed postcard.

Respectfully submitted,

DLA PIPER RUDNICK GRAY CARY US LLP

May 11, 2005
Date



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Trudy Gerovske

TRUDY GEROVSKE

PROVISIONAL TO UTILITY

APPLICATION

for

UNITED STATES LETTERS PATENT

on

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

by

Elias Meezan

Dennis J. Pillion

and

Edward T. Maggio

Sheets of Drawings: Three (3)
Docket No.: AEGIS1210

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ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now pending; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now pending. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

BACKGROUND INFORMATION

[0003] Therapeutic agents are often combined with various surfactants. Yet, surfactants are frequently irritating to the skin and other tissues, including mucosal membranes such as those found in the nose, mouth, eye, vagina, rectum, esophagus, intestinal tract, and the like. Many surfactants also cause proteins to denature, thus destroying their biological activity. Another serious limitation to the development and use of such agents is the ability to deliver them safely, non-invasively, efficiently and stably to the site of action. Therefore, an ideal enhancing surfactant will stabilize the therapeutic agent, be non-toxic and non-irritable to the skin or mucosal surfaces, and enhance the passage or absorption of the therapeutic agent through various membrane barriers without damaging the structural integrity and biological function of the membrane and increase bioavailability of the agent.

SUMMARY OF THE INVENTION

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug enhancing agents of the invention contain a non-toxic surfactant consisting of at least an alkyl glycoside and/or saccharide alkyl ester. One advantage of the therapeutic compositions of the invention is that they permit administration and delivery of the therapeutic agents with high bioavailabilities at concentrations of enhancing agents that are dramatically below their so-called "no observable adverse effect levels" (their NOAEL's) . Accordingly, the present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug molecules, low molecular weight peptides such as Exenatide, GLP-1 and the like , proteins, and non-peptide therapeutic polymers such as low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions

[0005] In one aspect, the present invention relates to a surfactant composition having at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed, mixed or blended with a therapeutic agent, a drug, or biologically active compound, the surfactant stabilizes the biological activity and increases the bioavailability of the drug.

[0006] Accordingly, in one aspect, the invention provides a therapeutic composition having at least one biologically active compound and at least one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester or sucrose ester and wherein the therapeutic composition stabilizes the biologically active compound for at least about 6 months, or more, and from about 4°C to about 25°C.

[0007] The invention also provides a method of administering a therapeutic composition having a surfactant including at least one alkyl glycoside and/or saccharide alkyl ester admixed, mixed, or blended with at least one therapeutic agent, or a drug, or biologically active compound, and administered or delivered to a subject, wherein the alkyl has from about 10 to 24, 10 to 20, 10 to 16, or 10 to 14 carbon atoms, wherein the surfactant increases the stability and bioavailability of the therapeutic agent.

[0008] In yet another aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering the compound via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route when admixed, mixed or blended with an absorption increasing amount of a suitable surfactant, wherein the surfactant is a nontoxic and nonionic hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. Such low molecular weight compounds include but are not limited to, nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

[0009] The present invention also provides a method of treating diabetes including administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell), a blood glucose reducing amount of a therapeutic composition, for example, an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of incretin mimetic agent or insulin and lowering the level of blood glucose and treating diabetes in the subject.

[0010] The present invention also provides a method of treating congestive heart failure in a subject including administering to the subject in need thereof via the oral, ocular, nasal, nasolacrimal, or inhalation delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a

hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0011] In another aspect, the invention provides a method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0012] In another aspect, the invention provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon when the route of administration is oral, ocular, nasal, or nasolacrimal.

[0013] The present invention also provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kilo Daltons (kD), with the proviso that the subject does not have diabetes when delivery is via the oral, ocular, nasal or nasolacrimal routes.

[0014] In one aspect of the invention, there is provided a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group

joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide (exendin-4) in a pharmaceutically acceptable carrier.

[0015] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

[0016] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

[0017] In one aspect, the invention provides a pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

[0018] In one aspect, the invention provides pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

[0019] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

[0020] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount

of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

[0021] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

[0022] In one aspect, the invention provides a method of increasing absorption of a compound into the CSF of a subject having administered intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide.

[0023] In yet another aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino

acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0024] In one aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering, via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

[0025] In one aspect, the invention provides a method of controlling caloric intake by administering a composition having a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0026] In another aspect, the invention provides a method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0027] Still, in another aspect, the invention provides a controlled release dosage composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 is a graph showing the intranasal percent bioavailability compared to intravenous injection and the subject-to-subject coefficients of variation for MIACALCIN® (salmon calcitonin) with and without alkyl glycoside.

[0029] Figure 2 is a graph showing the effect of intranasal administration of insulin/0.25%TDM (filled circles) and intranasal administration of insulin alone (open circles) in reducing blood glucose levels.

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25%TDM and IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following oral administration of glucose (i.e., in a so-called "glucose tolerance test").

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention may be understood more readily by reference to the following detailed description of specific embodiments and the Examples included therein.

[0032] The present invention is based on the discovery that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject.

[0033] A "therapeutic composition" can consist of an admixture with an organic or inorganic carrier or excipient, and can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, or other form suitable for use. The carriers, in addition to those disclosed above, can include glucose, lactose, mannose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition, auxiliary stabilizing, thickening or coloring agents can be used, for example a stabilizing dry agent such as triulose.

[0034] A "drug" is any therapeutic compound, or molecule, or therapeutic agent, or biologically active compound, including but not limited to nucleic acids, small molecules, proteins, polypeptides or peptides, etc. The term "nucleic acids" also denotes DNA, cDNA, RNA, siRNA, RNAi, etc. which encode translated and untranslated regions or inhibits translated or untranslated regions of structural genes encoding a peptide or protein of the invention. For example, a nucleic acid of the invention can include 5' and 3' untranslated regulatory nucleotide sequences as well as translated sequences associated with the structural gene, e.g. GLP-1.

[0035] A peptide of the invention may be any medically or diagnostically useful peptide or protein of small to medium size (i.e. up to about 15 kD, 30 kD, 40 kD, 50 kD, 60 kD, 70 kD, 80 kD, 90 kD, 100 kD, for example). The mechanisms of improved polypeptide absorption are described in U.S. Patent No. 5,661,130 which is hereby incorporated by reference in its entirety. Invention compositions can be mixed with all such peptides, although the degree to which the peptide benefits are improved may vary according to the molecular weight and the physical and chemical properties of the peptide, and the particular surfactant used. Examples of polypeptides include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone

(GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), prolactin, insulin, insulin like growth factor-I (IGF-I) somatomedin-C (SM-C), calcitonin, leptin and the leptin derived short peptide OB-3, melatonin, GLP-1 or Glucagon-like peptide-1,, GiP, neuropeptide pituitary adenylate cyclase, GM-1 ganglioside, nerve growth factor (NGF), nafarelin, D-tryp6)-LHRH, FGF, VEGF antagonists, leuprolide, interferon (e.g., α,β, γ) low molecular weight heparin, PYY, LHRH antagonists, Keratinocyte Growth Factor (KGF) , Glial-Derived Neurotrophic Factor (GDNF), ghrelin, and ghrelin antagonists. Further, in some aspects, the peptide or protein is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

[0036] Other drugs or therapeutic compounds, molecules and/or agents include compounds or molecules of the central nervous system affecting neurotransmitters or neural ion channels (i.e. antidepressants (bupropion)), selective serotonin 2c receptor agonists, anti-seizure agents (topiramate, zonisamide), some dopamine antagonists, and cannabinoid-1 receptor antagonists (rimonabant)); leptin/insulin/central nervous system pathway agents (i.e. leptin analogues, leptin transport and/or leptin receptor promoters, ciliary neurotrophic factor (Axokine), neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin, cocaine and amphetamine regulated transcript promoters, alpha-melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor-gamma receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin); gastrointestinal-neural pathway agents (i.e. agents that increase glucagon-like peptide-1 activity (extendin-4, liraglutide, dipeptidyl peptidase IV inhibitors), protein YY3-36, ghrelin, ghrelin antagonists, amylin analogues (pramlintide)); and compounds or molecules that may increase resting metabolic rate "selective" beta-3 stimulators/agonist, melanin concentrating hormone antagonists,

phytostanol analogues, functional oils, P57, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11B-hydroxysteroid dehydrogenase type 1 activity, corticotropin-releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, and gastrointestinal lipase inhibitors (ATL962).

[0037] The therapeutic composition of the invention includes a drug and a drug absorption enhancing agent, for example, a surfactant. The term "surfactant" is any surface active agent that modifies interfacial tension of water. Typically, surfactants have one lipophilic and one hydrophilic group in the molecule. Broadly, the group includes soaps, detergents, emulsifiers, dispersing and wetting agents, and several groups of antiseptics. More specifically, surfactants include stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glycerin monostearate; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

[0038] Preferably, the surfactant of the invention consists of at least one suitable alkyl glycoside. As used herein, "alkyl glycoside" refers to any sugar joined by a linkage to any hydrophobic alkyl, as is known in the art. Any "suitable" alkyl glycoside means one that fulfills the limiting characteristics of the invention, i.e., that the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route. Suitable compounds can be determined using the methods set forth herein.

[0039] Alkyl glycosides of the invention can be synthesized by known procedures, i.e., chemically, as described, e.g., in Rosevear et al., *Biochemistry* 19:4108-4115 (1980) or Koeltzow and Urfer, *J. Am. Oil Chem. Soc.*, 61:1651-1655 (1984), U.S. Pat. No. 3,219,656 and U.S. Pat. No. 3,839,318 or enzymatically, as described, e.g., in Li et al., *J. Biol. Chem.*, 266:10723-10726 (1991) or Gopalan et al., *J. Biol. Chem.* 267:9629-9638 (1992).

[0040] Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl- α- or β-D-maltoside, -glucoside or -sucroside (synthesized according to Koeltzow and Urfer; Anatrace Inc., Maumee, Ohio; Calbiochem, San Diego, Calif.; Fluka Chemie, Switzerland); alkyl thiomaltosides, such as heptyl, octyl, dodecyl-, tridecyl-, and tetradecyl-β-D-thiomaltoside (synthesized according to Defaye, J. and Pederson, C., "Hydrogen Fluoride, Solvent and Reagent for Carbohydrate Conversion Technology" in Carbohydrates as Organic Raw Materials, 247-265 (F. W. Lichtenthaler, ed.) VCH Publishers, New York (1991); Ferenci, T., J. Bacteriol, 144:7-11 (1980)); alkyl thioglucosides, such as heptyl- or octyl 1-thio α- or β-D-glucopyranoside (Anatrace, Inc., Maumee, Ohio; see Saito, S. and Tsuchiya, T. Chem. Pharm. Bull. 33:503-508 (1985)); alkyl thiosucroses (synthesized according to, for example, Binder, T. P. and Robyt, J. F., Carbohydr. Res. 140:9-20 (1985)); alkyl maltotriosides (synthesized according to Koeltzow and Urfer); long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers; (synthesized according to Austrian Patent 382,381 (1987); Chem. Abstr., 108:114719 (1988) and Gruber and Greber pp. 95-116); derivatives of palatinose and isomaltamine linked by amide linkage to an alkyl chain (synthesized according to Kunz, M., "Sucrose-based Hydrophilic Building Blocks as Intermediates for the Synthesis of Surfactants and Polymers" in Carbohydrates as Organic Raw Materials, 127-153); derivatives of isomaltamine linked by urea to an alkyl chain (synthesized according to Kunz); long chain aliphatic carbonic acid ureides of sucrose β-amino-alkyl ethers (synthesized according to Gruber and Greber, pp. 95-116); and long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers (synthesized according to Austrian Patent 382,381 (1987), Chem. Abstr., 108:114719 (1988) and Gruber and Greber, pp. 95-116).

[0041] Surfactants of the invention consisting of an alkyl glycoside and/or a sucrose ester have characteristic hydrophile-lipophile balance (HLB) numbers, which can be calculated or determined empirically (Schick, M. J. Nonionic Surfactants, p. 607 (New York: Marcel Dekker, Inc. (1967)). The HLB number is a direct reflection of the

hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. HLB numbers can be calculated by the formula: (20 times MW hydrophilic component)/(MW hydrophobic component+MW hydrophilic component), where MW=molecular weight (Rosen, M. J., Surfactants and Interfacial Phenomena, pp. 242-245, John Wiley, New York (1978)). The HLB number is a direct expression of the hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. A preferred surfactant has an HLB number of from about 10 to 20 and an even more preferred range of from about 11 to 15.

[0042] As described above, the hydrophobic alkyl can thus be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety. For example, one preferred range of alkyl chains is from about 9 to about 24 carbon atoms. An even more preferred range is from about 9 to about 16 or about 14 carbon atoms. Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

[0043] The surfactants of the invention can also include a saccharide. As use herein, a "saccharide" is inclusive of monosaccharides, oligosaccharides or polysaccharides in straight chain or ring forms, or a combination thereof to form a saccharide chain. Oligosaccharides are saccharides having two or more monosaccharide residues. The saccharide can be chosen, for example, from any currently commercially available saccharide species or can be synthesized. Some examples of the many possible saccharides to use include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Preferable saccharides include maltose, sucrose and glucose.

[0044] The surfactants of the invention can likewise consist of a sucrose ester. As used herein, "sucrose esters" are sucrose esters of fatty acids and is a complex of sucrose and fatty acid. Sucrose esters can take many forms because of the eight hydroxyl groups in

sucrose available for reaction and the many fatty acid groups, from acetate on up to larger, more bulky fatty acids that can be reacted with sucrose. This flexibility means that many products and functionalities can be tailored, based on the fatty acid moiety used. Sucrose esters have food and non-food uses, especially as surfactants and emulsifiers, with growing applications in pharmaceuticals, cosmetics, detergents and food additives. They are biodegradable, non-toxic and mild to the skin.

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a hydrophobic saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

[0046] The above examples are illustrative of the types of glycosides to be used in the methods claimed herein, but the list is not exhaustive. Derivatives of the above compounds which fit the criteria of the claims should also be considered when choosing a glycoside. All of the compounds can be screened for efficacy following the methods taught herein and in the examples.

[0047] The compositions of the present invention can be administered in a format selected from the group consisting of a tablet, a capsule, a suppository, a drop, a spray, an aerosol and a sustained release or delayed burst format. The spray and the aerosol can be achieved through use of an appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive

microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J. Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss. The prolonged drug contact is non-toxic to the skin and mucosal surfaces.

[0048] The surfactant compositions of the invention are stable. For example, Baudys et al. in U.S. Patent No. 5,726,154 show that calcitonin in an aqueous liquid composition comprising SDS (sodium dodecyl sulfate, a surfactant) and an organic acid is stable for at least 6 months. Similarly, the surfactant compositions of the present invention have improved stabilizing characteristics when admixed with a drug. No organic acid is required in these formulations. For example, the composition of the invention maintains the stability of proteins and peptide therapeutics for about 6 months, or more, when maintained at about 4°C to 25°C.

[0049] The stability of the surfactant compositions are, in part, due to their high no observable adverse effect level (NOAEL). The Environmental Protection Agency (EPA) defines the no observable adverse effect level (NOAEL) as the exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Hence, the term, "no observable adverse effect level" (or NOAEL) is the greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions.

[0050] The Food and Agriculture Organization (FAO) of the United Nations of the World Health Organization (WHO) has shown that some alkyl glycosides have very high NOAELs, allowing for increased consumption of these alkyl glycosides without any adverse effect. This report can be found on the world wide web at inchem.org/documents/jecfa/jecmono/v10je11.htm. For example, the NOAEL for sucrose dodecanoate, a sucrose ester used in food products, is about 20-30 grams/kilogram/day,

e.g. a 70 kilogram person (about 154 lbs.) can consume about 1400 - 2100 grams (or about 3 to 4.6 pounds) of sucrose dodecanoate per day without any observable adverse effect. Typically, an acceptable daily intake for humans is about 1% of the NOAEL, which translates to about 14–21 grams, or 14 million micrograms to 21 million micrograms, per day, indefinitely. Definitions of NOAELs and other related definitions can be found on the world wide web at epa.gov/OCEPAterms. Thus, although some effects may be produced with alkyl glycoside levels anticipated in the present invention, the levels are not considered adverse, or precursors to adverse effects.

[0051] Accordingly, a subject treated with surfactant compositions of the invention having at least one alkyl glycoside, e.g. tetradecylmaltoside (TDM; or Intravail A), at a concentration of about 0.125% by weight of alkyl glycoside two times per day, or three times per day, or more depending on the treatment regimen consumes about 200 to 300 micrograms per day total of TDM. So, the effective dose of the TDM is at least 1000X fold lower than (i.e., 1/1000) of the NOAEL, and falls far below 1% of the NOAEL, which is the acceptable daily intake; or in this case about 1/50,000 of the acceptable daily intake.. Stated another way, alkyl glycosides of the present invention have a high NOAEL, such that the amount or concentration of alkyl glycosides used in the present invention do not cause an adverse effect and can be safely consumed without any adverse effect.

[0052] The surfactant compositions of the invention are also stable because they are physiologically non-toxic and non-irritants. The term, "nontoxic" means that the alkyl glycoside molecule has a sufficiently low toxicity to be suitable for human administration and consumption. Preferred alkyl glycosides are non-irritating to the tissues to which they are applied. Any alkyl glycoside used should be of minimal or no toxicity to the cell, such that it does not cause damage to the cell. Yet, toxicity for any given alkyl glycoside may vary with the concentration of alkyl glycoside used. It is also beneficial if the alkyl glycoside chosen is metabolized or eliminated by the body and if this metabolism or elimination is done in a manner that will not be harmfully toxic. The term, "non-irritant" means that the agent does not cause inflammation following immediate, prolonged or repeated contact with the skin surface or mucous membranes.

[0053] Moreover, one embodiment of the surfactant compositions, in particular, the sucrose esters, serve as anti-bacterial agents. An agent is an "anti-bacterial" agent or substance if the agent or its equivalent destroy bacteria, or suppress bacterial growth or reproduction. The anti-bacterial activity of sucrose esters and their fatty acids have been reported. Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508. Watanabe et al. (2000) describe that galactose and fructose laureates are particularly effective carbohydrate monoesters. Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213. Hence, the present invention is not limited to the sucrose ester described herein, but encompasses other carbohydrate esters, including galactose and fructose esters, that suppress bacterial growth and reproduction.

[0054] The surfactant compositions of the invention are typically present at a level of from about 0.01% to 20% by weight. More preferred levels of incorporation are from about 0.01% to 5% by weight, from about 0.01% to 2% by weight, from about 0.01% to 1%, most preferably from about 0.01% to 0.125% by weight. The surfactant is preferably formulated to be compatible with other components present in the composition. In liquid, or gel, or capsule, or injectable, or spray compositions the surfactant is most preferably formulated such that it promotes, or at least does not degrade, the stability of any protein or enzyme in these compositions. Further, the invention optimizes the concentration by keeping the concentration of absorption enhancer as low as possible, while still maintaining the desired effect.

[0055] The compositions of the invention when administered to the subject, yield enhanced mucosal delivery of the biologically active compound(s), or drug, with a peak concentration (or Cmax) of the compound(s) in a tissue, or fluid, or in a blood plasma of the subject that is about 15%, 20%, or 50% or greater as compared to a Cmax of the compound(s) in a tissue (e.g. CNS), or fluid, or blood plasma following intramuscular injection of an equivalent concentration of the compound(s) to the subject.

[0056] The measure of how much of the drug or compound(s) reaches the bloodstream in a set period of time, e.g. 24 hours can also be calculated by plotting drug blood concentration at various times during a 24-hour or longer period and then measuring the area under the curve (AUC) between 0 and 24 hours. Similarly, a measure of drug efficacy can also be determined from a time to maximal concentration (tmax) of the biologically active compound(s) in a tissue (e.g. CNS) or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours. The therapeutic compositions of the invention increase the speed of onset of drug action (i.e., reduce Tmax) by a factor of about 1.5-fold to 2-fold.

[0057] Also, the therapeutic compositions or formulations of the invention can be administered or delivered to a subject in need systemically or locally. Suitable routes may, for example, include oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), transmucosal administration, vaginal, rectal, parenteral delivery, including intramuscular, subcutaneous, intravenous, intraperitoneal, or CSF delivery. Moreover, the mode of delivery e.g. liquid, gel, tablet, spray, etc. will also depend on the method of delivery to the subject.

[0058] Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant, emollient, lubricant, stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a solvent, emulsifier, gelling agent, moisturizer, stabilizer, wetting agent, time release agent, humectant, or other component commonly included in a particular form of pharmaceutical composition. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, and oils such as olive oil or injectable organic esters. A pharmaceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize or to increase the absorption of the specific inhibitor, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or

glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. A pharmaceutically acceptable carrier can also be selected from substances such as distilled water, benzyl alcohol, lactose, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, titanium dioxide, and flavoring agents.

[0059] Additionally, to decrease susceptibility of alkyl saccharides or saccharide alkyl esters to hydrolytic cleavage of the drug, various oxygen atoms within the drugs can be substituted for by sulfur (Defaye, J. and Gelas, *J. in Studies in Natural Product Chemistry* (Atta-ur-Rahman, ed.) Vol. 8, pp. 315-357, Elsevier, Amsterdam, 1991). For example, the heteroatom of the sugar ring can be either oxygen or sulfur, or the linkage between monosaccharides in an oligosaccharide can be oxygen or sulfur (Horton, D. and Wander, J. D., "Thio Sugars and Derivatives," The Carbohydrates: Chemistry and Biochemistry, 2d. Ed. Vol. IB, (W. Reyman and D. Horton eds.), pp. 799-842, (Academic Press, New York), (1972)). Oligosaccharides can have either α (alpha) or β (beta) anomeric configuration (see Pacsu, E., et al. in Methods in Carbohydrate Chemistry (R. L. Whistler, et al., eds.) Vol. 2, pp. 376-385, Academic Press, New York 1963).

[0060] A composition of the invention can be prepared in tablet form by mixing a therapeutic agent or drug and one alky glycoside and/or saccharide alkyl ester according to the invention, and an appropriate pharmaceutical carrier or excipient, for example mannitol, corn starch, polyvinylpyrrolidone or the like, granulating the mixture and finally compressing it in the presence of a pharmaceutical carrrier such as corn starch, magnesium stearate or the like. If necessary, the formulation thus prepared may include a sugar-coating or enteric coating or covered in such a way that the active principle is released gradually, for example, in the appropriate pH medium.

[0061] The term "enteric coating," is a polymer encasing, surrounding, or forming a layer, or membrane around the therapeutic composition or core. Also, the enteric coating can contain a drug which is compatible or incompatible with the coating. One tablet composition may include an enteric coating polymer with a compatible drug which

dissolves or releases the drug at higher pH levels (e.g., pH greater than 4.0, greater than 4.5, greater than 5.0 or higher) and not at low pH levels (e.g., pH 4 or less); or the reverse.

[0062] In a preferred embodiment, the dose dependent release form of the invention is a tablet comprising:

(a) a core comprising:

(i) a therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is an impermeable, permeable, semi-permeable or porous coating and becomes more permeable or porous upon contacting an aqueous environment of a defined pH.

[0063] The term "membrane" is synonymous with "coating," or equivalents thereof. The terms are used to identify a region of a medicament, for example, a tablet, that is impermeable, permeable, semi-permeable or porous to an aqueous solution(s) or bodily fluid(s), and/or to the therapeutic agent(s) or drug(s) encapsulated therein. If the membrane is permeable, semi-permeable or porous to the drug, the drug can be released through the openings or pores of the membrane in solution or *in vivo*. The porous membrane can be manufactured mechanically (e.g., drilling microscopic holes or pores in the membrane layer using a laser), or it can be imparted due to the physiochemical properties of the coating polymer(s). Membrane or coating polymers of the invention are well known in the art, and include cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3 ,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference.

[0064] Further, the enteric coating according to the invention can include a plasticizer, and a sufficient amount of sodium hydroxide (NaOH) to effect or adjust the pH of the

suspension in solution or *in vivo*. Examples of plasticizers include triethyl citrate, triacetin, tributyl sebecate, or polyethylene glycol. Other alkalizing agents, including potassium hydroxide, calcium carbonate, sodium carboxymethylcellulose, magnesium oxide, and magnesium hydroxide can also be used to effect or adjust the pH of the suspension in solution or *in vivo*.

[0065] Accordingly, in one embodiment, an enteric coating can be designed to release a certain percentage of a drug or drugs in certain mediums with a certain pH or pH range. For example, the therapeutic composition of the invention may include at least one enteric coating encasing or protecting at least one drug which is chemically unstable in an acidic environment (e.g., the stomach). The enteric coating protects the drug from the acidic environment (e.g., pH < 3), while releasing the drug in locations which are less acidic, for example, regions of the small and large intestine where the pH is 3, or 4, or 5, or greater. A medicament of this nature will travel from one region of the gastrointestinal tract to the other, for example, it takes about 2 to about 4 hours for a drug to move from the stomach to the small intestine (duodenum, jejunum and ileum). During this passage or transit, the pH changes from about 3 (e.g., stomach) to 4, or 5, or to about a pH of 6 or 7 or greater. Thus, the enteric coating allows the core containing the drug to remain substantially intact, and prevents premature drug release or the acid from penetrating and de-stabilizing the drug.

[0066] Examples of suitable enteric polymers include but are not limited to cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl

acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof. One skilled in the art will appreciate that other hydrophilic, hydrophobic and enteric coating polymers may be readily employed, singly or in any combination, as all or part of a coating according to the invention.

[0067] The therapeutic compositions of the invention in the form of a tablet can have a plurality of coatings, for example, a hydrophilic coating (e.g., hydroxypropylmethyl-cellulose), and/or a hydrophobic coating (e.g., alkylcelluloses), and/or an enteric coating. For example, the tablet core can be encases by a plurality of the same type of coating, or a plurality of different types of coating selected from a hydrophilic, hydrophobic or enteric coating. Hence, it is anticipated that a tablet can be designed having at least one, but can have more than one layer consisting of the same or different coatings dependent on the target tissue or purpose of the drug or drugs. For example the tablet core layer may have a first composition enclosed by a first coating layer (e.g. hydrophilic, hydrophobic, or enteri-coating), and a second same or different composition or drug having the same or different dosage can be enclosed in second coating layer, etc. This layering of various coatings provides for a first, second, third, or more gradual or dose dependent release of the same or different drug containing composition.

[0068] In a preferred embodiment, a first dosage of a first composition of the invention is contained in a tablet core and with an enteric-coating such that the enteric-coating protects and prevents the composition contained therein from breaking down or being released into the stomach. In another example, the first loading dose of the therapeutic composition is included in the first layer and consists of from about 10% to about 40% of the total amount of the total composition included in the formulation or tablet. In a second

loading dose, another percentage of the total dose of the composition is released. The invention contemplates as many time release doses as is necessary in a treatment regimen. Thus, in certain aspects, a single coating or plurality of coating layers is in an amount ranging from about 2% to 6% by weight, preferably about 2% to about 5%, even more preferably from about 2% to about 3% by weight of the coated unit dosage form.

[0069] Accordingly, the composition preparations of the invention make it possible for contents of a hard capsule or tablet to be selectively released at a desired site the more distal parts of the gastro-intestinal tract (e.g. small and large intestine) by selecting the a suitable pH-soluble polymer for a specific region. Mechanical expulsion of the composition preparations may also be achieved by inclusion of a water absorbing polymer that expands upon water absorption within a hard semi-permeable capsule thus expelling composition through an opening in the hard capsule.

[0070] Drugs particularly suited for dose dependent time release include but are not limited to insulin like growth factor-I (IGF-I), somatomedin-C (SM-C; diabetes, nerve function, renal function), insulin (diabetes), calcitonin (osteoporosis), leptin (obesity; infertility), leptin derived short peptide (OB-3), hGH (AIDs wasting, dwarfism), human parathyroid hormone (PTH) (osteoporosis), melatonin (sleep), GLP-1 or Glucagon-like peptide-1 (diabetes), GiP (diabetes), pituitary adenylate cyclase-activating polypeptide (PACAP) and islet function (diabetes), GM-1 ganglioside, (Alzheimers), nerve growth factor (NGF), (Alzheimers), nafarelin (endometriosis), Synarel® (nafarelin acetate nasal solution), (D-tryp6)-LHRH (fertility), FGF (duodenal ulcer, macular degeneration, burns, wounds, spinal cord injuries, repair of bone and cartilage damage), VEGF antagonists (to block the receptor), VEGF (agonist) neonatal distress syndrome; ALS), leuprolide (prostate and breast cancer), interferon-alpha (chronic hepatitis C), low molecular weight heparin (blood clotting, deep vein thrombosis), PYY (obesity), LHRH antagonists (fertility), LH (luteinizing hormone), ghrelin antagonists (obesity), KGF (Parkinson's), GDNF (Parkinsons), G-CSF (erythropoiesis in cancer), Imitrex (migraine), Integrelin (anticoagulation), Natrecor® (congestive heart failure), human B-type natriuretic peptide (hBNP), SYNAREL® (Searl; nafarelin acetate nasal solution), Sandostatin (growth

hormone replacement), Forteo (osteoporosis), DDAVP® Nasal Spray (desmopressin acetate), Cetrotide® (cetrorelix acetate for injection), Antagon™ (ganirelix acetate), Angiomax (bivalirudin; thrombin inhibitor), Accolate® (zafirlukast; injectable), Exendin-4 (Exanatide; diabetes), SYMLIN® (pramlintide acetate; synthetic amylin; diabetes), desmopressin, glucagon, ACTH (corticotrophin), C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, tobramycin ocular (corneal infections), Vasopressin, desmopresin, Fuzeon (Roche; HIV fusion inhibitor MW 4492), and Eptifibatide.

[0071] Further, it will be understood by one skilled in the art, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0072] It has been shown that alkyl glycosides, particularly alkylmaltosides and more specifically, dodecylmaltoside (DDM) and tetradecylmaltoside (TDM), stabilize insulin in solution and prevent aggregation of the peptide. Hovgaard et al., "Insulin Stabilization and GI absorption," *J. Control. Rel.*, 19 (1992) 458-463, *cited in* Hovgaard et al., "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132 (1996) 107-113 (hereinafter, "Hovgaard-1"). Further, Hovgaard-1 shows that even after 57 days, the DDM-insulin complex remained stable and possessed nearly full biological activity. It is postulated that the stability of the complex is due to the length of the alkyl group (number of carbon atoms) and the higher ratio of DDM to insulin ratio the better (e.g. 4:1 and 16:1; see FIG. 1 in Hovgaard 1). However, according to Hovgaard-1, although the DDM-insulin complex was stable, the same stability was not shown for other maltosides. Yet, in a related study, Hovgaard et al.(1996) demonstrated

that when DDM-insulin was orally administered to animals *in vivo*, bioavailability of the complex was weak (e.g. 0.5% - 1% bioavailability). Hovgaard et al., "Stabilization of insulin by alkylmaltoside. B. Oral absorption in vivo in rats," *Int. J. Pharmaceutics* 132 (1996) 115-121 (Hovgaard-2). Hence, an improved aspect of the invention is that the surfactant increases the bioavailability of a drug to the target tissues, organs, system etc., as well as increase drug stability.

[0073] Accordingly, one aspect of the invention is to provide therapeutic compositions having at least one drug and one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester formulation which enhances the bioavailability of the drug. Determining the bioavailability of drug formulations is described herein. As used herein, "bioavailability" is the rate and extent to which the active substance, or moiety, which reaches the systemic circulation as an intact drug. The bioavailability of any drug will depend on how well is adsorbed and how much of it escapes being removed from the liver.

[0074] To determine absolute bioavailability, the tested drug and mode of administration is measured against an intravenous reference dose. The bioavailability of the intravenous dose is 100% by definition. For example, animals or volunteering humans are given an intravenous injections and corresponding oral doses of a drug. Urinary or plasma samples are taken over a period of time and levels of the drug over that period of time are determined.

[0075] The areas under the curve (AUC), of the plasma drug concentration versus time curves, are plotted for both the intravenous and the oral doses, and calculation of the bioavailability of both formulations is by simple proportion. For example, if the same intravenous and oral doses are given, and the oral AUC is 50% of the intravenous AUC, the bioavailability of the oral formulation is 50%. Note that the bioavailability of any drug is due to many factors including incomplete absorption, first pass clearance or a combination of these (discussed more below). Further, the peak concentration (or C_{max}) of the plasma drug concentration is also measured to the peak concentration (C_{max}) of the

plasma drug concentration following intramuscular (IM) injection of an equivalent concentration the drug. Moreover, the time to maximal concentration (or t_{max}) of the plasma drug is about 0.1 to 1.0 hours.

[0076] To determine the relative bioavailability of more than one formulation of a drug (e.g. an alkyl glycoside or saccharide alkyl ester drug formulation), bioavailability of the formulations are assessed against each other as one or both drugs could be subject to first pass clearance (discussed more below) and thus undetected. For example, a first oral formulation is assessed against a second oral formulation. The second formulation is used as a reference to assess the bioavailability of the first. This type of study provides a measure of the relative performance of two formulations in getting a drug absorbed.

[0077] Bioavailabilities of drugs are inconsistent and vary greatly from one drug to the next. For example, the bioavailability of MIACALCIN® (salmon calcitonin from Novartis) nasal spray, a prescription medication for the treatment of postmenopausal osteoporosis in women, has a mean bioavailability of about 3% (range is 0.3%-30.6%; see FIG. 1). The MIACALCIN® product information sheet can be found on the world wide web at miacalcin.com/info/howWorks/index.jsp and drugs.com/PDR/Miacalcin_Nasal_Spray.html. The data on MIACALCIN®, which was obtained by various investigators using different methods and human subjects, show great variability in the drug's bioavailability, e.g. in normal volunteers only ~3% of the nasally administered dose is bioavailable, as compared to the same dose administered by intramuscular injection (MIACALCIN® product insert). This represents two orders of a magnitude in variability and is undesirable to the consumer.

[0078] Poor bioavailability of a drug can also be observed in NASCOBAL® (Nastech), or cyanocobalamin, which is used for the treatment and maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B_{12} therapies. The gel formulation was administered intranasally and the bioavailability of B_{12} was compared to intramuscular B_{12} injections. The peak concentrations of B_{12} (or the Tmax) was reached in 1-2 hours after intranasal administration, and relative to the intramuscular

injection, the bioavailability of B_{12} nasal gel was found to be about 8.9% (90% confidence intervals, 7.1% to 11.2%).

[0079] The alkyl glycosides or sucrose esters of the present invention include any compounds now known or later discovered. Drugs which are particularly well suited for admixture with the alkyl glycosides and/or saccharide alkyl esters of the invention are those that are difficult to administer by other methods, e.g. drugs that are degraded in the gastrointestinal (GI) tract or those that are not absorbed well from the GI tract, or drugs that can be self-administered via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route instead of traditional methods such as injection. Some specific examples include peptides, polypeptides, proteins, nucleic acids and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone, and human growth hormone or other low molecular weight peptides and proteins.

[0080] Alternatively, bioavailability of a drug can be determined by measuring the levels of the drug's first pass clearance by the liver. Alkyl glycosides and/or saccharide alkyl ester compositions of the invention administered intranasally or via oral cavity (sublingual or Buccal cell) do not enter the hepatic portal blood system, thereby avoiding first pass clearance by the liver. Avoiding first past clearance of these formulations by the liver is described herein. The term, "first pass liver clearance" is the extent to which the drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation. This is also called first pass metabolism or first pass extraction.

[0081] The two major routes of drug elimination from the body are excretion by the kidneys whereby the drug is unchanged; and elimination by the liver, whereby the drug is metabolized. The balance between these two routes depends on the relative efficiency of the two processes. The present invention describes herein elimination by the liver or liver

clearance. First pass liver clearance is described by Birkett et al (1990 and 1991), which is incorporated by reference in its entirety. Birkett et al., *Aust Prescr,* 13(1990):88-9; and Birkett et al., *Austra Prescr* 14:14-16 (1991).

[0082] Blood carrying drug from the systemic circulation enter the liver via the portal vein, and the liver in turn extracts a certain percentage or ratio (i.e. 0.5 or 50%) of that drug. The remainder left over (i.e. 0.2 or 20%) re-enters the systemic circulation via the hepatic vein. This rate of clearance of the drug is called the hepatic extraction ratio. It is the fraction of the drug in the blood which is irreversibly removed (or extracted) during the first pass of the blood through the liver. If no drug is extracted, the hepatic extraction ratio is zero. Conversely, if the drug is highly extracted in the first pass through the liver, the hepatic extraction ratio may be as high as 100% or 1.0. In general, clearance of the drug by the liver depends then on the rate of delivery of that drug to the liver (or the hepatic blood flow), and on the efficiency of removal of that drug (or the extraction ratio).

[0083] Therefore, the net equation used to determine hepatic clearance is:

(hepatic clearance – blood flow) = (unbound fraction * intrinsic clearance) / blood flow + (unbound fraction * intrinsic clearance) **(1)**

[0084] The "unbound fraction" of drug is dependent on how tightly the drug is bound to proteins and cells in the blood. In general, it is only this unbound (or free) drug which is available for diffusion from the blood into the liver cell. In the absence of hepatic blood flow and protein binding, the "intrinsic clearance" is the ability of the liver to remove (or metabolize) that drug. In biochemical terms, it is a measure of liver enzyme activity for a particular drug substrate. Again, although intrinsic clearance can be high, drugs cannot be cleared more rapidly than that presented to the liver. In simple terms, there are two situations: where liver enzyme activity is very high or very low (i.e. high extraction ratio or low extraction ratio).

[0085] When liver enzyme activity is low, the equation simplifies to:

hepatic clearance = unbound fraction * intrinsic clearance **(2)**

[0086] Clearance then is independent of blood flow, but instead depends directly on the degree of protein binding in the blood and the activity of drug metabolizing enzymes towards that drug.

[0087] In contrast, when liver enzyme activity is high, the equation is:

hepatic clearance = liver blood flow **(3)**

[0088] In this scenario, because the enzymes are so active the liver removes most of the drug presented to it and the extraction ratio is high. Thus, the only factor determining the actual hepatic clearance is the rate of supply of drug to the liver (or hepatic blood flow).

[0089] First pass liver clearance is important because even small changes in the extraction of drugs can cause large changes in bioavailability. For example, if the bioavailability of drug A by oral administration is 20% by the time it reaches the systemic circulation, and the same drug A by intravenous administration is 100%, absent no other complicating factors, the oral dose will therefore have to be 5 times the intravenous dose to achieve similar plasma concentrations.

[0090] Secondly, in some instances where liver enzyme activity is very high, drug formulations should be designed to have the drug pass directly through to the systemic circulation and avoid first pass liver clearance all together. For example, drugs administered intranasally, sublingual, buccal, rectal, vagina, etc. directly enter the systemic circulation and do not enter the hepatic portal blood circulation to be partially or fully extracted by the liver. Alternatively, where drugs cannot be administered by the above means, a tablet with at least one enteric-coating layer to prevent release of the drug in the stomach (i.e. highly acidic environment) is provided. Thus, an objective of the invention is to administer drugs using these alternative routes.

[0091] Additionally, first pass liver clearance is an important factor because many patients are on more than one drug regimen, and this may cause drug interactions which increase or decrease liver enzyme activity; thereby increasing or decreasing metabolism (increasing or decreasing the hepatic extraction ratio) of the drug of interest.

[0092] Hence, therapeutic compositions of the invention can be administered directly to the systemic circulatory system and avoid first pass liver clearance. Avoiding first pass clearance assures that more of the drug will be available to the system. Stated another way, by avoiding first pass liver clearance, the bioavailability of the drug is increased.

[0093] The present invention also relates to methods of increasing absorption of a low molecular compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, or the CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

[0094] The composition formulation is appropriately selected according to the administration route, such as oral administration (oral preparation), external administration (e.g., ointment), injection (preparations for injection), and mucosal administration (e.g., buccal and suppository) etc. For example, excipients (e.g., starch, lactose, crystalline cellulose, calcium lactate, magnesium aluminometasilicate and anhydrous silicate), disintegrators (e.g., carboxymethylcellulose and calcium carboxymethylcellulose), lubricants (e.g., magnesium stearate and talc), coating agents (e.g., hydroxyethylcellulose), and flavoring agents can be used for oral and mucosal formulations; whereas, solubilizers and auxiliary solubilizers capable of forming aqueous injections (e.g., distilled water for injection, physiological saline and propylene glycol), suspending agents (e.g., surfactant such as polysorbate 80), pH regulators (e.g., organic acid and metal salt thereof) and stabilizers are used for injections; and aqueous or oily solubilizers and auxiliary solubilizers (e.g., alcohols and fatty acid esters), tackifiers (e.g., carboxy vinyl polymer and polysaccharides) and emulsifiers (e.g., surfactant) are used for external agents. The drug and the alkyl glycoside can be admixed, mixed, or blended along with the above

excipients, disintegrators, coating polymers, solubilizers, suspending agents, etc., prior to administration, or they can be administered sequentially, in either order. It is preferred that they be mixed prior to administration.

[0095] The term, "mucosal delivery-enhancing agent" includes agents which enhance the release or solubility (e.g., from a formulation delivery vehicle), diffusion rate, penetration capacity and timing, uptake, residence time, stability, effective half-life, peak or sustained concentration levels, clearance and other desired mucosal delivery characteristics (e.g., as measured at the site of delivery, or at a selected target site of activity such as the bloodstream or central nervous system) of a compound(s) (e.g., biologically active compound). Enhancement of mucosal delivery can occur by any of a variety of mechanisms, including, for example, by increasing the diffusion, transport, persistence or stability of the compound, increasing membrane fluidity, modulating the availability or action of calcium and other ions that regulate intracellular or paracellular permeation, solubilizing mucosal membrane components (e.g., lipids), changing non-protein and protein sulfhydryl levels in mucosal tissues, increasing water flux across the mucosal surface, modulating epithelial junction physiology, reducing the viscosity of mucus overlying the mucosal epithelium, reducing mucociliary clearance rates, and other mechanisms.

[0096] Exemplary mucosal delivery enhancing agents include the following agents and any combinations thereof:

(a) an aggregation inhibitory agent;
(b) a charge-modifying agent;
(c) a pH control agent;
(d) a degradative enzyme inhibitory agent;
(e) a mucolytic or mucus clearing agent;
(f) a ciliostatic agent;
(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0097] Additional mucosal delivery-enhancing agents include, for example, citric acid, sodium citrate, propylene glycol, glycerin, ascorbic acid (e.g., L-ascorbic acid), sodium metabisulfite, ethylenediaminetetraacetic acid (EDTA) disodium, benzalkonium chloride, sodium hydroxide, and mixtures thereof.

[0098] Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.

[0099] The mechanisms of improved drug absorption according to the invention are generally applicable and should apply to all such peptides or protein, although the degree to which their absorption is improved may vary according to the molecular weight (MW) and the physico-chemical properties of the peptide or protein, and the particular enhancer used. Examples of peptides or protein include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), and prolactin.

[0100] One preferred composition of the invention is the peptide drug is Exenatide (or exendin-4) and an alkyl glycoside. Exenatide is a synthetic version of exendin-4, and has been used in clinical trials by Amylin™ Pharmaceuticals. Exendin-4 is a low molecular weight peptide that is the first of a new class of therapeutic medications known as incretin mimetic agents or hormones. Incretin hormones are any of various gastrointestinal (GI) hormones and factors that act as potent stimulators of insulin secretion, e.g. as gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), or Exenatide, or exendin-4, or equivalents thereof.

[0101] Exendin-4 is a naturally occurring 39-amino acid peptide isolated from salivary secretions of the Gila Monster Lizard. Eng et al., "Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas," *J. Biol. Chem.* 267(15):7402-7405(1992). Exenatide exhibits similar glucose lowering actions to glucagons like peptide, or GLP-1. Exenatide is being investigated for its potential to address important unmet medical needs of many people with type 2 diabetes. Clinical trials suggest that Exenatide treatment decreases blood glucose toward target levels and is associated with weight loss. The effects on glucose control observed with Exenatide

treatment are likely due to several actions that are similar to those of the naturally occurring incretin hormone GLP-1 (see Example 7). These actions include stimulating the body's ability to produce insulin in response to elevated levels of blood glucose, inhibiting the release of glucagon following meals and slowing the rate at which nutrients are absorbed into the bloodstream. In animal studies Exenatide administration resulted in preservation and formation of new beta cells, the insulin-producing cells in the pancreas, which fail as type 2 diabetes progresses.

[0102] Use of Exenatide, incretin mimetic agents or equivalents thereof can be used to treat various forms of diabetes including but not limited to brittle diabetes, chemical diabetes or impaired glucose tolerance, gestational diabetes, diabetes insipidus, diabetes insipidus central, diabetes insipidus nephrogenic, diabetes insipidus pituitary, latent diabetes, lipatrophic diabetes, maturity-onset diabetes of youth (MODY), diabetes mellitus (DM), diabetes mellitus adult-onset (type 2 DM), diabetes mellitus insulin-dependent (IDDM, or type 1 DM), diabetes mellitus non-insulin dependent (NIDDM), diabetes mellitus juvenile or juvenile-onset, diabetes mellitus ketosis-prone, diabetes mellitus ketosis-resistant, diabetes mellitus malnutrition-related (MRDM), diabetes mellitus tropical or tropical pancreatic, diabetes mellitus, preclinical diabetes, or diabetes induced by various drugs e.g. thiazide diabetes, steroid diabetes, or various diabetes animal model including but not limited to alloxan diabetes and puncture diabetes.

[0103] In another aspect, therapeutic compositions of the invention are used to treat obesity. Obesity is a common problem in both adults and adolescents. For example, PYY3-36 (or AC162352) is a hormone that plays a critical role in decreasing appetites. The gut hormone fragment peptide PYY3–36 (PYY) reduces appetite and food intake when infused into subjects of normal weight. Similar to the adipocyte hormone, leptin, PYY reduces food intake by modulating appetite circuits in the hypothalamus. However, in obese patients there is a resistance to the action of leptin, thereby limiting leptin's therapeutic effectiveness. Still other studies show that PYY reduces food intake. Injection of PYY revealed that they eat on average 30% less than usual, resulting in weight loss.

Hence, PYY 3-36 has potential as a treatment for obesity. Amylin™ Pharmaceuticals submitted an Investigational New Drug application for PYY 3-36 in 2003.

[0104] Compounds whose absorption can be increased by the method of this invention include any compounds now known or later discovered, in particular drugs, or therapeutic compounds, molecules or agents that are difficult to administer by other methods, for example, drugs that are degraded in the gastrointestinal (GI) tract or that are not absorbed well from the GI tract, or drugs that subjects could administer to themselves more readily via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route than by traditional self-administration methods such as injection. Some specific examples include peptides, polypeptides, proteins and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone (PTH), and human growth hormone or other low molecular weight peptides and proteins.

[0105] Further, the therapeutic compositions of the invention also contemplate non-peptide drugs or therapeutic agents. For example, in U.S. Pat. No. 5,552,534, non-peptide compounds are disclosed which mimic or inhibit the chemical and/or biological activity of a variety of peptides. Such compounds can be produced by appending to certain core species, such as the tetrahydropyranyl ring, chemical functional groups which cause the compounds to be at least partially cross-reactive with the peptide. As will be recognized, compounds which mimic or inhibit peptides are to varying degrees cross-reactivity therewith. Other techniques for preparing peptidomimetics are disclosed in U.S. Pat. Nos. 5,550,251 and 5,288,707. The above U.S. patents are incorporated by reference in their entirety.

[0106] The method of the invention can also include the administration, along with the alkyl glycoside and a protein or peptide, a protease or peptidase inhibitor, such as

aprotinin, bestatin, alpha$_1$ proteinase inhibitor, soybean trypsin inhibitor, recombinant secretory leucocyte protease inhibitor, captopril and other angiotensin converting enzyme (ACE) inhibitors and thiorphan, to aid the protein or peptide in reaching its site of activity in the body in an active state (i.e., with degradation minimal enough that the protein is still able to function properly). The protease or peptidase inhibitor can be mixed with the alkyl glycoside and drug and then administered, or it can be administered separately, either prior to or after administration of the glycoside or drug.

[0107] The invention also provides a method of lowering blood glucose level in a subject comprising administering a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose. A "blood glucose-reducing amount" of such a composition is that amount capable of producing the effect of reducing blood glucose levels, as taught herein. Preferred is an amount that decreases blood glucose to normoglycemic or near normoglycemic range. Also preferred is an amount that causes a sustained reduction in blood glucose levels. Even more preferred is an amount sufficient to treat diabetes, including diabetes mellitus (DM) by lowering blood glucose level. Thus, the instant method can be used to treat diabetes mellitus. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0108] Also provided is a method of raising blood glucose level in a subject by administering a blood glucose-raising amount comprising glucagons and at least one alkyl glycoside and/or saccharide alkyl ester. When the composition includes insulin, it can be used to cause the known effect of insulin in the bloodstream, i.e., lower the blood glucose levels in a subject. Such administration can be used to treat diabetes mellitus, or related diseases. A "blood glucose-raising amount" of glucagon in such a composition is that amount capable of producing the effect of raising blood glucose levels. A preferred amount is that which increases blood glucose to normoglycemic or near-normoglycemic range. Another preferable amount is that which causes a sustained rising of blood glucose

levels. Even more preferred, is that amount which is sufficient to treat hypoglycemia by raising blood glucose level. Thus, this method can be used to treat hypoglycemia. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0109] Similarly, when this composition includes glucagon, it can be used to cause the known effect of glucagon in the bloodstream, i.e., to raise the blood glucose levels in a subject. Such administration can therefore be used to treat hypoglycemia, including hypoglycemic crisis.

[0110] The invention also provides methods for ameliorating neurological disorders which comprises administering a therapeutic agent to the cerebral spinal fluid (CSF). The term "neurological disorder" denotes any disorder which is present in the brain, spinal column, and related tissues, such as the meninges, which are responsive to an appropriate therapeutic agent. The surprising ability of therapeutic agents of the present invention to ameliorate the neurological disorder is due to the presentation of the therapeutic agent to persist in the cerebro-ventricular space. The ability of the method of the invention to allow the therapeutic agent to persist in the region of the neurological disorder provides a particularly effective means for treating those disorders.

[0111] It will be understood, however, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Generally, however, dosage will approximate that which is typical for known methods of administration of the specific compound. For example, for intranasal administration of insulin, an approximate dosage would be about 0.5 unit/kg regular porcine insulin (Moses et al.). Dosage for compounds affecting blood glucose levels optimally would be that required to achieve proper glucose levels, for example, to a normal range of about 5-6.7 mM. Additionally, an

appropriate amount may be determined by one of ordinary skill in the art using only routine testing given the teachings herein (see Examples).

[0112] Furthermore, the compositions of the invention can be administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained release format. The spray and the aerosol can be achieved through use of the appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J. Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss.

[0113] The present invention is more particularly described in the following examples which are intended as illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art. The following examples are intended to illustrate but not limit the invention.

EXAMPLE 1

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER FORMULATIONS DO NOT CAUSE MUCOSA IRRITATION OR DISRUPTION

[0114] The nasal mucosa is highly vascularized and hence optimal for high drug permeation. Moreover, absorption of drug(s) through the nasal mucosa is available to the central nervous system (CNS). Although local application of drugs is desirable, a challenge for this method of administration is mucosal irritancy.

[0115] A formulation consisting of an alkyl glycoside (0.125% TDM) in a commercial over-the-counter (OTC) nasal saline was administered *in vivo* to human nasal epithelium over a period of over one month. The 0.125% TDM formulation is compared to the control, namely the same commercial (OTC) nasal saline, over the same period of time.

Results show that during and after 33 days of daily TDM administration (i.e., the duration of the study), there is no observable irritation of the nasal mucosa (data not shown). Thus, compositions of the invention are non-toxic and non-irritable providing repeated and long-term intranasal administration, which is beneficial for those patients with chronic and ongoing disease(s).

[0116] A similar test was performed using sucrose dodecanoate, a sucrose ester. Sucrose dodecanoate is administered *in vivo* to human nasal epithelium and during and after 47 days (i.e., the duration of the study), no observable irritation was detected (data not shown). Thus, these results show that alkyl glycosides and sucrose esters of the invention are non-toxic and do not cause mucosa irritation when administered daily over a long period of time.

EXAMPLE 2

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER COMPOSITIONS STABILIZE DRUGS BY INCREASING DRUG BIOAVAILABILITY AND REDUCING DRUG BIOAVAILABILITY VARIANCE

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

[0118] Figure 1 is a graph comparing the bioavailability of the drug MIACALCIN® (salmon calcitonin from Novartis) with and without alkyl glycoside (TDM). MIACALCIN® is a nasal spray and administered directly onto the nasal epithelium or nasal mucosa. Figure 1 shows that MIACALCIN® minus alkyl glycoside has very low bioavailability levels in humans (MIACALCIN® product specification insert), as compared to the MIACALCIN® with alkyl glycoside as administered to rats. More specifically, intranasal delivery of MIACALCIN® with 0.125% and 0.250% alkyl glycoside (TDM) resulted in about 43% to about 90% bioavailability, respectively. The bioavailability of intranasal administration of MIACALCIN® without alkyl glycoside is only about 3% in humans, and was undetectable in rats, suggesting that the rat is a stringent model for estimating intranasal drug absorption in humans. Thus, the alkyl glycoside of the invention enhances absorption and increases bioavailability of the drug.

[0119] Furthermore, besides increasing the bioavailability of the drug, the alkyl glycoside compositions of the invention effectively decrease the bioavailability variance of the drug. Figure 1 shows that administration of MIACALCIN® with alkyl glycoside (0.125% or 0.25%) intranasally has a bioavailability variance of +/- 8%, whereas the bioavailability variance without alkyl glycoside is 0.3% to 30%, or a two orders of magnitude change. The increase in bioavailability and the decrease in the bioavailability variance ensures patient-to-patient variability is also reduced. The results as shown in FIG. 1 are administered intranasally, however, similar results are expected for oral, buccal, vaginal, rectal, etc. delivery and at different alkyl glycoside concentrations.

[0120] Thus, contrary to the art, the alkyl glycoside compositions of the invention, in the range of about 0.01% to about 6% result in increased bioavailability and reduced bioavailability variance. This has not otherwise been reported.

EXAMPLE 3

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0121] Normal rats were anesthetized with a mixture of xylazine/ketamine to elevate their blood glucose levels. The elevated levels of D-glucose that occur in response to anesthesia provide an optimal system to measure the systemic hypoglycemic action of drug administration, e.g. insulin-containing eye drops. This animal model mimics the hyperglycemic state seen in diabetic animals and humans. In the experimental animal group, anesthetized rats are given eye drops containing insulin. Blood glucose levels from the experimental group are compared to anesthetized animals which received eye drops without insulin. The change in blood glucose levels and the differential systemic responses reflects the effect of insulin absorbed via the route of administration, e.g. ocular route.

[0122] Adult male Sprague-Dawley rats (250-350g) were fed *ad libitum*, and experiments were conducted between 10:00 a.m. and 3:00 p.m. Rats were anesthetized with a mixture of xylazine (7.5 mg/kg) and ketamine (50 mg/kg) given intraperitoneally (IP) and allowed to stabilize for 50-90 min before the administration of eye drops. Anesthesia of a normal rat with xylazine/ketamine produces an elevation in blood glucose values which provides an optimal state to determine the systemic hypoglycemic action of insulin-containing eye drops. Blood D-glucose values were measured by collecting a drop of blood from the tail vein at 5-10 min intervals throughout the experiment and applying the blood to glucometer strips (Chemstrip bG) according to directions provided with the instrument (Accu-Chek II, Boehringer Mannheim Diagnostics; Indianapolis, Ind.). Blood D-glucose values ranged from 200 to 400 mg/dl in anesthetized nondiabetic rats.

[0123] At time 0, after a 50-90 min stabilization period, rats were given 20 µl of eye drops composed of phosphate-buffered saline (PBS) with or without 0.2% regular porcine insulin and 0.125%-0.5% of the absorption enhancing alkyl glycoside (e.g. TDM) to be tested. Eye drops were instilled at time 0 using a plastic disposable pipette tip with the eyes held open, and the rat was kept in a horizontal position on a warming pad (37°C.)

throughout the protocol. The rats were given additional anesthesia if they showed signs of awakening. Rats received in each eye 20 µl of 0.125-0.5% absorption enhancer in phosphate buffered saline, pH 7.4 with (experimental) or without (control) 0.2% (50 U/ml) regular porcine insulin (Squibb-Novo, Inc.) for a total of 2 U per animal. Octyl-β-D-maltoside, decyl-β-D-maltoside, dodecyl-µ-D-maltoside, tridecyl-β-D-maltoside and tetradecyl-β-D-maltoside were obtained from Anatrace, Inc. (Maumee, Ohio). Hexylglucopyranoside, heptylglucopyranoside, nonylglucopyranoside, decylsucrose and dodecylsucrose were obtained from Calbiochem, Inc. (San Diego, Calif.); Saponin, BL-9 and Brij 78 were obtained from Sigma Chemical Co. (St. Louis, Mo.).

[0124] The D-glucose levels in the blood remained elevated when the animals received eye drops containing: 1) saline only; 2) 0.2% regular porcine insulin in saline only; or 3) absorption enhancer only. However, when rats received eye drops containing 0.2% regular porcine insulin and several alkylmaltoside or alkylsucrose compounds, a pronounced decrease in blood D-glucose values occurred and was maintained for up to two hours. Insulin administered ocularly with 0.5% dodecyl-β-D-maltoside (see Table I) or 0.5% decyl-β-D-maltoside (see Table III) results in a prompt and sustained fall in blood glucose levels which are maintained in the normoglycemic (80-120 mg/dl) or near-normoglycemic (120-160 mg/dl) range for the two hour duration of the experiment. Hence, at least two alkylmaltosides are effective in achieving sufficient absorption of insulin delivered via the ocular route to produce a prompt and sustained fall in blood glucose levels in experimentally hyperglycemic animals. The surfactant compositions of the invention are therefore useful to achieve systemic absorption of insulin and other peptides/proteins, e.g., glucagon and macromolecular drugs and heparin delivered via the ocular route in the form of eye drops.

[0125] Several other alkylmaltosides are also effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table III) and 0.125% (Table II) and 0.5% tetradecyl maltoside. These studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl- and

tetradecyl-β-D-maltosides, are more effective. The increase in the number of carbon atoms also contributes to the greater hydrophobic/hydrophilic structural balance and absorption enhancing effect. The shorter alkyl chains (fewer carbon atoms) e.g., decylmaltoside, or no, e.g., octylmaltoside, produce less absorption enhancing activity. It is noted that the most effective alkylmaltosides produce effects comparable to or greater than those seen with other absorption enhancers such as saponin, and with the added advantage that they can be metabolized to nontoxic products following systemic absorption.

[0126] The effects of the alkylmaltosides as absorption enhancers are dose-dependent, as can be seen by examining the effects of different concentrations ranging from 0.125-0.5% in producing a hypoglycemic effect when combined with insulin. Whereas, 0.5% and 0.375% dodecylmaltoside appear equally effective in achieving systemic absorption of insulin and reduction of blood glucose levels, 0.25% has a smaller and more transient effect and 0.125% is ineffective (Table I). Similarly, tridecylmaltoside also shows a dose-dependent effect in lowering blood glucose concentrations when combined with insulin, but the effect achieved with even 0.25% of the absorption enhance is sustained for the two hour time course of the experiment. Thus, dose-dependent effects of the alkylmaltosides suggest that they achieve enhancement of protein absorption via the ocular route in a graded fashion proportional to the concentration of the agent.

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

[0127] The absorption enhancing effects of the alkyl saccharides were not confined to the alkylmaltosides alone since dodecylsucrose (0.125%, 0.25%, 0.375%) also shows a dose-dependent effect in producing ocular absorption of insulin and reduction in blood glucose levels. This effect is observed even at 0.125% alkyl saccharide (from 335 mg/dl.+-.26 mg/dl at time 0 min. to 150 mg/dl +-.44 mg/dl at time 120 min.). 0.5% decylsucrose was also effective in reducing blood glucose levels, but as shown for the alkylmaltosides, a reduction in the length of the alkyl chain, and hence the hydrophobic properties of the molecule, appears to reduce the potency of the alkylsucrose compounds. However, a significant and sustained reduction in blood glucose levels is achieved with 0.5% decylsucrose (from 313 mg/dl.+-.15 mg/dl at time 0 min. to 164 mg/dl+-.51 mg/dl at time 120 min.). The absorption enhancing abilities of alkyl saccharides with two distinct disaccharide moieties suggests that it is the physicochemical properties of the compounds which are crucial to their activity and that other alkyl saccharides, e.g., dodecyllactose, have the right balance of properties to be equally or more effective as absorption

enhancers while retaining the metabolic and nontoxic properties of the alkylsaccharide enhancing agents. These alkyl saccharides are anticipated by the invention.

[0128] Studies with alkylglucosides were also conducted; 0.5% hexylglucoside and 0.5% heptylglucoside were ineffective at promoting insulin absorption from the eye, but 0.5% nonylglucoside effectively stimulated insulin absorption and reduced blood glucose levels (from 297 mg/dl to 150 mg/dl). This result once further supports that the alkyl chain length, as well as the carbohydrate moiety, play critical roles in effectively enhancing insulin absorption.

[0129] It should be noted that no damaging effects (i.e. non-irritants) to the ocular surface were observed with any of the alkylmaltoside or alkylsucrose agents employed in these studies. Furthermore, the prompt and sustained hypoglycemic effects produced by these agents in combination with insulin suggest that these absorption enhancers do not adversely affect the biological activity of the hormone, in keeping with their nondenaturing, mild surfactant properties.

[0130] Thus, therapeutic compositions on the invention consisting of at least an alkyl glycoside and a drug are stable and the alkyl glycosides enhance the absorption of the drug.

EXAMPLE 4

OCULAR AND INTRANASAL ADMINISTRATION OF TDM PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0131] Since previous Examples showed that administration via eye drops of an absorption enhancer with drug e.g. insulin results in significant absorption of the drug via the nasolacrimal drainage system, therapeutically effective administration of insulin with alkylmaltosides, alkylsucrose and like agents by intranasal administration is tested herein.

[0132] Tetradecylmaltoside (TDM) in combination with insulin also produced a drop in blood D-glucose levels when administered in the form of a drop intranasally as well as via

a drop by the ocular route. Eye drops containing 0.2% regular porcine insulin with 0.125% tetradecylmaltoside are administered to rats as previously described. The administration of the composition produces a prompt and prominent drop in blood glucose levels. The drop in blood glucose levels decrease even more by administration of a nose drop containing the same concentration of insulin with 0.5% tetradecylmaltoside (Table II). Thus, intranasal delivery and administration of the alkyl saccharide with drug results in lowering of blood glucose levels.

TABLE II

Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Time (min)	Blood Glucose (mg/dl)
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

EXAMPLE 5

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

[0133] Previous studies demonstrated that insulin absorption from the eye is stimulated by saponin, BL-9 and Brij-78. BL-9 and Brij-78 are ineffective at stimulating the absorption of glucagon from the eye, whereas saponin is effective. Glucagon absorption from the eye was measured in rats given eye drops containing various surfactants plus glucagon (30 μg) (Eli Lilly, Indianapolis, Indiana) by monitoring an elevation in blood D-glucose levels. In these experiments, rats were anesthetized with sodium pentobarbital rather than xylazine/ketamin. This modification of the procedure resulted in basal blood glucose levels in the normoglycemic range and made it possible to readily monitor the hyperglycemic action of any glucagon absorbed from the eye.

[0134] Paired animals that receive eye drops containing the surfactant alone, or glucagon alone, were compared to animals receiving eye drops with the surfactant plus glucagon. When eyedrops containing 0.5% saponin plus glucagon are administered to rats, the level of D-glucose in blood rises significantly, but no such effect is observed with eye drops containing 0.5% BL-9 or 0.5% Brij-78 plus glucagon. Interestingly, when eye drops containing dodecylsucrose, decylmaltose or tridecylmaltose plus glucagon are administered to rats which were previously treated with eye drops containing these surfactant agents plus insulin, the glucagon is absorbed and blood D-glucose values increase significantly (Table III). This result confirms that ocular administration of certain alkylsaccharides can enhance the absorption of drugs, including glucagon and insulin. Moreover, it is now possible to treat for a hypoglycemic crisis using a formulation with at least an alkyl saccharide of the invention.

TABLE III

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Time (min)	Blood Glucose Concentration (mg/dl)		
-20	266	249	255
-10	305	287	307
	Insulin Eye Drops Added		
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
	Glucagon Eye Drops Added		
130	111	95	82
140	143	99	121
150	202	132	148
160	247	157	173
170	242	171	162
180	234	180	162
190	211	189	156

EXAMPLE 6

INTRANASAL ADMINISTRATION OF 0.25% TDM PLUS INSULIN DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0135] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in

Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase in the blood glucose levels as shown in FIG. 2 (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhibition of pancreatic insulin secretion. Blood glucose levels peak to about 482 mg/dl by 30 minutes after the xylazine-ketamine injection (FIG. 2). Then, at approximately 33 minutes after the xylazine-ketamine injection, 6 μL of insulin (Humalog) in 0.25% tetradecylmaltoside (TDM; or Intravail A) was administered intranasally using a long thin micropipette tip, and blood glucose levels were monitored at about 15 minute intervals. After administration of the 0.25% TDM/insulin composition, there was a rapid decrease in blood glucose levels, reaching a low of about 80 mg/dl at about the 60 minute time point, or about 30 minutes after the insulin administration (FIG. 2). At about the 75 minute time point, blood glucose levels gradually returned to the baseline level in a normoglycemic mouse, or about 80-100 mg/dl.

[0136] The results above were compared with animals treated with insulin alone (same dosage), minus 0.25% TDM (FIG.2, open circles). The insulin only treatment showed blood glucose levels do not start to decline until at about the 120 minute time mark, or about 110 minutes after the insulin administration. Further, the blood glucose levels observed in animals treated with insulin alone never return to normoglycemic levels, as was observed in those animals receiving insulin plus 0.25%TDM (FIG. 2).

[0137] Thus, these results again demonstrate that compositions of the invention consisting of certain alkyl glycosides or alkyl saccharides plus a drug, e.g. insulin, effectively lower blood glucose levels, and that these effects are measurable shortly after administration of the drug.

EXAMPLE 7

INTRANASAL ADMINISTRATION OF 0.25% TDM (INTRAVAIL A) + EXENDIN-4 DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0138] The ob/ob mouse model was utilized for the studies described herein. Friedman, J. M. , *Nature* 404, 632-634 (2000). All animals received an intraperitoneal (IP) injection of a bolus of 2 g/kg glucose for purposes of determining glucose tolerance. At time 0 the experimental animals were given about 100 micrograms/kg of exendin-4/0.25% TDM (exendin-4 from American Peptide) either as 10 µl of nasal drops (FIG. 3; closed triangles), or by IP injection (FIG. 3; closed circles), or by and IP injection of saline alone (no drug, no TDM; FIG. 3; open circles). Control animals were previously performed and received no drugs. The results of this study are shown in FIG. 3.

[0139] Figure 3 shows that glucose tolerance of the animals were different since blood glucose levels vary at time 0 when the animals received the glucose bolus. Regardless, of the glucose tolerance level at time 0, immediately after injection of the glucose bolus, blood glucose levels increased in all three animals. The blood glucose level of the animal receiving the IP injection of saline alone does not decrease as rapidly as the experimental animals receiving the drug. Moreover, the animal receiving the IP injection of saline alone never reached a normoglycemic level (FIG.3, open circles). In contrast, the experimental animals, after administration of nasal drops of exendin-4/TDM, or IP injection of exendin-4/TDM, showed a rapid and immediate decrease in blood glucose levels.

[0140] Also exendin-4 administered about 15-30 minutes ahead of the glucose bolus (before time 0 in FIG. 3; data not shown) produced an even more pronounced lowering of blood glucose effect, because the absorption of the hormone takes a certain amount of time to be absorbed and to be active. Thus, exendin-4 (or Exenatide) which is currently in human clinical trials, when combined with alkyl glycosides of the invention, effectively treats a hyperglycemic condition by lowering the blood glucose levels of the hyperglycemic subject.

[0141] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Birkett et al., (1991) "Bioavailability and first pass clearance," *Austra Prescr* 14:14-16.

Birkett et al., (1990) "How drugs are cleared by the liver," *Austra Prescr* 3:88-89.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132:107-113.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides. B. Oral absorption *in vivo* in rats," *Int. J. Pharmaceutics* 132:115-121.

Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213.

[0142] Although the present process has been described with reference to specific details of certain embodiments thereof in the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

What is claimed is:

1. A surfactant composition comprising of at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed with a drug, the surfactant stabilizes the biological activity and increases the bioavailability, of the drug.

2. The composition of claim 1, wherein the drug is a peptide or a protein.

3. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than the daily intake amount of the surfactant.

5. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than the daily intake amount of the surfactant.

6. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 1000 times higher than the daily intake amount of the surfactant.

7. The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system.

13. The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 20%.

15. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 5%.

16. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 2%.

17. A therapeutic composition comprising of at least one biologically active compound(s) and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside and/or saccharide alkyl ester and wherein said composition stabilizes the biological activity of the drug, for at least about 6 months from about 4°C to 25°C.

18. The composition of claim 17, wherein the pH of the composition is less than 8.0.

19. The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. The composition of claim 17, wherein the composition concentration is from about 0.01% to 20%.

21. The composition of claim 17, wherein the composition concentration is from about 0.01% to 5%.

22. The composition of claim 17, wherein the composition concentration is from about 0.01% to 2%.

23. A stable therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. A stable therapeutic composition according to claim 17, wherein the administration to the subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of said biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of said subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to said subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to the subject.

27. The therapeutic composition of claim 17, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active compound(s) in said CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater compared to an AUC of said biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to said subject.

28. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields an area under concentration curve (AUC) of said biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. A method of administering a drug composition comprising of a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

32. The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than the daily intake amount of the surfactant.

34. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than the daily intake amount of the surfactant.

35. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than the daily intake amount of the surfactant.

36. The method of claim 31, wherein the surfactant reduces the bioavailability variance from patient to patient.

37. The method of claim 31, wherein the composition does not enter the hepatic portal blood system.

38. The method of claim 31, wherein the pH of the composition is less than 8.0.

39. The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. The method of claim 31, wherein the composition concentration is from about 0.01% to 20%.

41. The method of claim 31, wherein the composition concentration is from about 0.01% to 5%.

42. The method of claim 31, wherein the composition concentration is from about 0.01% to 2%.

43. The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. The method of claim 1, wherein the composition is further comprised of an enteric coating.

45. The method of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM).

46. The method of claim 45, wherein the TDM has anti-bacterial activity.

47. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route, the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

48. The method of claim 47, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

49. The method of claim 47, wherein the alkyl has from 9 to 24 carbons.

50. The method of claim 49, wherein the alkyl has from 9 to 14 carbon atoms.

51. The method of claim 50, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

52. The method of claim 47, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

53. The method of claim 47, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

54. The method of claim 47, wherein the compound is a protein or a peptide.

55. The method of claim 54, and further comprising administering a protease or peptidase inhibitor.

56. The method of claim 47, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

57. The method of claim 47, wherein the composition is an intranasal spray.

58. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

59. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.1 mL per administered dose.

60. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 20 μg.

61. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

62. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

63. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

64. The method of claim 47, wherein the composition is an intranasal spray.

65. The method of claim 47, wherein the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

66. The method of claim 47, wherein the composition comprises a total volume of about 0.1 mL per administered dose.

67. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per administered dose.

68. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

69. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

70. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

71. A method of claim 47, wherein the composition is administered within 60 minutes before a meal.

72. A method of claim 47, wherein the composition is in the form of a single or unit dose and comprising no preservatives.

73. A method of claim 47, wherein the compound further comprises a polymeric coating selected from a group consisting of a hydrophilic, hydrophobic or enteric coating.

74. A method of claim 47, wherein the coating is an enteric coating.

75. A method of claim 47, wherein the enteric coating is selected from selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

76. A method of treating diabetes comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a blood glucose reducing amount of a

composition comprising an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the effectiveness of incretin mimetic agent or insulin and lowering the level of blood glucose and treating the diabetes in the subject.

77. The method of claim 76, wherein the subject has Type-2 diabetes.

78. The method of claim 76, wherein the subject is a human.

79. The method of claim 76, wherein the incretin mimetic is Exenatide.

80. A method of treating congestive heart failure in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

81. A method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

82. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, pulmonary, oral cavity (sublingual, Buccal cell), or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon.

83. The method of claim 82, wherein the compound has a molecular weight of less than about 15 kD.

84. The method of claim 82, wherein the compound is selected from vasopressin, a vasopressin polypeptide analog, desmopressin, glucagon, corticotropin, gonadotropin, C-peptide of insulin, parathyroid hormone, human growth hormone, growth hormone, growth hormone releasing hormone, oxytocin, corticotropin releasing hormone, somatostatin, a somatostatin polypeptide analog, gonadotropin agonist, a gonadotropin agonist polypeptide analog, atrial natriuretic peptide, thyroxine releasing hormone, follicle stimulating hormone, or prolactin.

85. The method of claim 82, wherein the compound is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

86. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the subject does not have diabetes.

87. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide in a pharmaceutically acceptable carrier.

88. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

89. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

90. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

91. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

92. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

93. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

94. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

95. A method as in claims 47-94 for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

96. A method for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent as in claims 87-95 such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

97. A method of increasing absorption of a compound into the CSF of a subject comprising administering intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

98. The method of claim 97, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

99. The method of claim 97, wherein the alkyl has from 9 to 24 carbons.

100. The method of claim 97, wherein the alkyl has from 9 to 14 carbon atoms.

101. The method of claim 97, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

102. The method of claim 97, wherein the compound is a protein or a peptide.

103. The method of claim 102, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

104. The method of claim 97, and further comprising administering a protease or peptidase inhibitor.

105. The method of claim 97, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

106. A method of controlling caloric intake by administering a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of TDM alkyl saccharide.

107. A method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

108. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent wherein the mucosal delivery-enhancing agent is selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents

provides for increased bioavailability of the compound in a blood plasma of a subject.

109. The pharmaceutical composition of claim 108, further comprising a plurality of intranasal delivery-enhancing agents.

110. The pharmaceutical composition of claim 108, wherein said mucosal delivery-enhancing agent(s) is/are selected from the group consisting of citric acid, sodium citrate, propylene glycol, glycerin, L-ascorbic acid, sodium metabisulfite, EDTA disodium, benzalkonium chloride, sodium hydroxide and mixtures thereof.

111. The pharmaceutical composition of claim 108, wherein the alkyl has from 10 to 16 carbon atoms.

112. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering, via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

113. The method of claim 112, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

114. The method of claim 112, wherein the alkyl has from 9 to 24 carbons.

115. The method of claim 112, wherein the alkyl has from 9 to 14 carbon atoms.

116. The method of claim 112, wherein the alkyl has from 10 to 16 carbon atoms.

117. The method of claim 112, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

118. The method of claim 112, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

119. The method of claim 112, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

120. The method of claim 112, wherein the compound is a protein or a peptide.

121. The method of claim 112, wherein the method comprises a protease or peptidase inhibitor.

122. The method of claim 112, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

123. The method of claim 112, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

124. A dosage dependent release composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

125. The membrane coating of claim 124 further comprising an alkalizing agent and/or a plasticizer.

126. The composition of claim 124 wherein the core is in the form of a tablet, hard capsule or gel capsule.

127. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 7.

128. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 6.

129. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 5.

130. The composition of claim 124, wherein the coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

131. The composition of claim 124, wherein the drug is selected from a group consisting of insulin like growth factor-I (IGF-I), somatomedin-C (SM-C), insulin, calcitonin, leptin, leptin derived short peptide (OB-3), hGH, human parathyroid hormone (PTH), melatonin, GLP-1 or Glucagon-like peptide-1, GiP, pituitary adenylate cyclase-activating polypeptide (PACAP), GM-1 ganglioside, nerve growth factor (NGF), nafarelin, Synarel®, (D-tryp6)-LHRH, FGF, VEGF antagonists, VEGF agonist, leuprolide, interferon-alpha, low molecular weight heparin, PYY, LHRH antagonists, LH, ghrelin antagonists, KGF, GDNF, G-CSF, Imitrex, Integrelin, Natrecor®, human B-type natriuretic peptide (hBNP), SYNAREL®, Sandostatin, Forteo, DDAVP® Nasal Spray, Cetrotide®, Antagon™, Angiomax, Accolate®, Exendin-4, SYMLIN®, desmopressin, glucagon, ACTH, C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone

releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, or tobramycin ocular.

132. The composition of claim 124, wherein the coating is a porous coating.

133. The composition of claim 124, further comprising a protease inhibitor.

134. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 24 carbon atoms.

135. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 20 carbon atoms.

136. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 16 carbon atoms.

137. The composition of claim 124, wherein the alkyl group has from about 10 to 14 carbon atoms.

138. The composition of claim 124, wherein the alkyl glycoside is tetradecyl maltoside (TDM).

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

ABSTRACT OF THE DISCLOSURE

A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

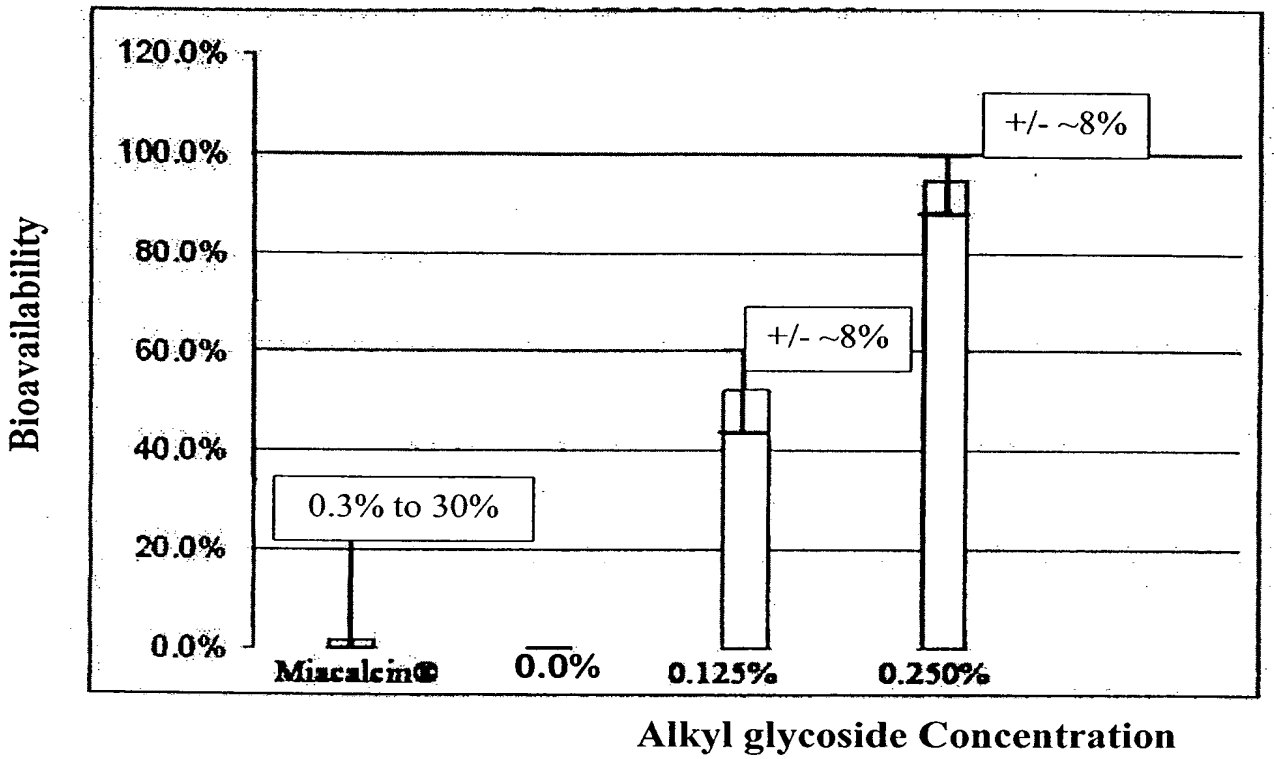


FIG. 1

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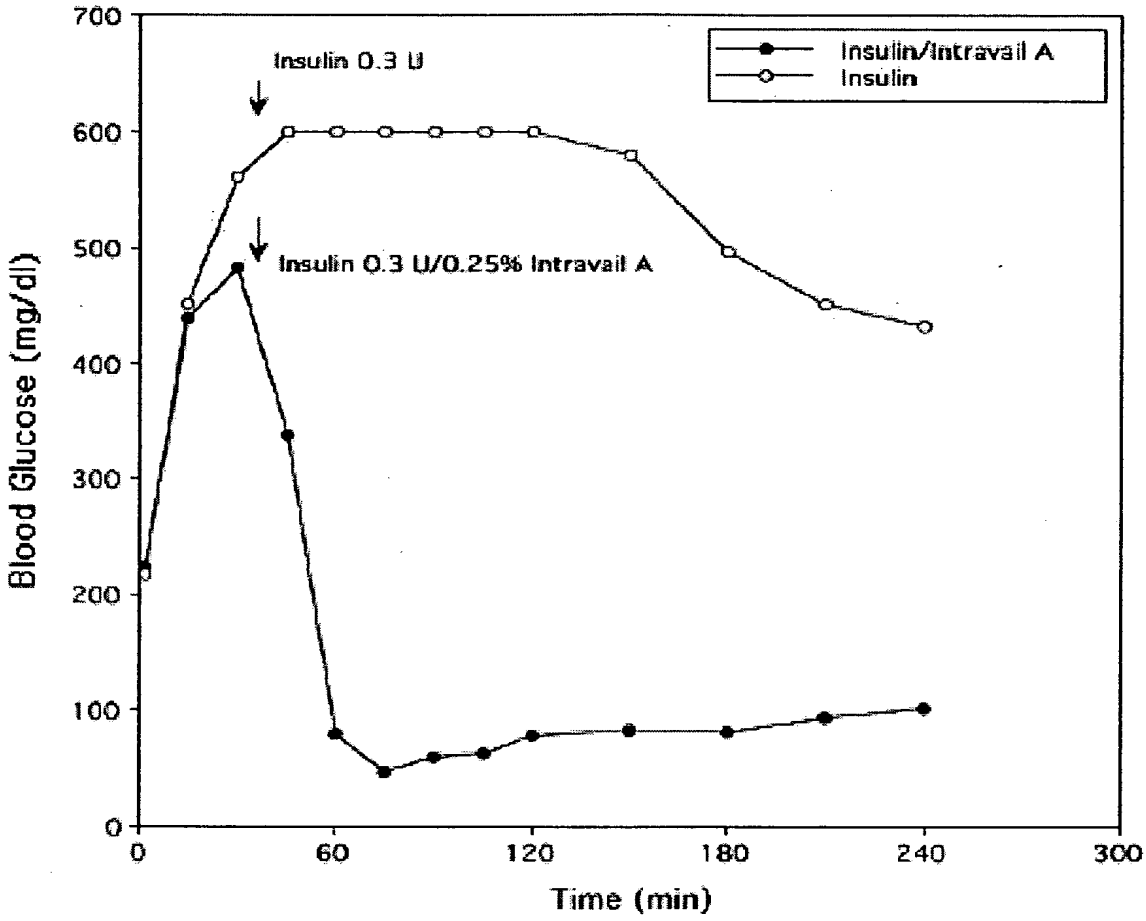


FIG. 2

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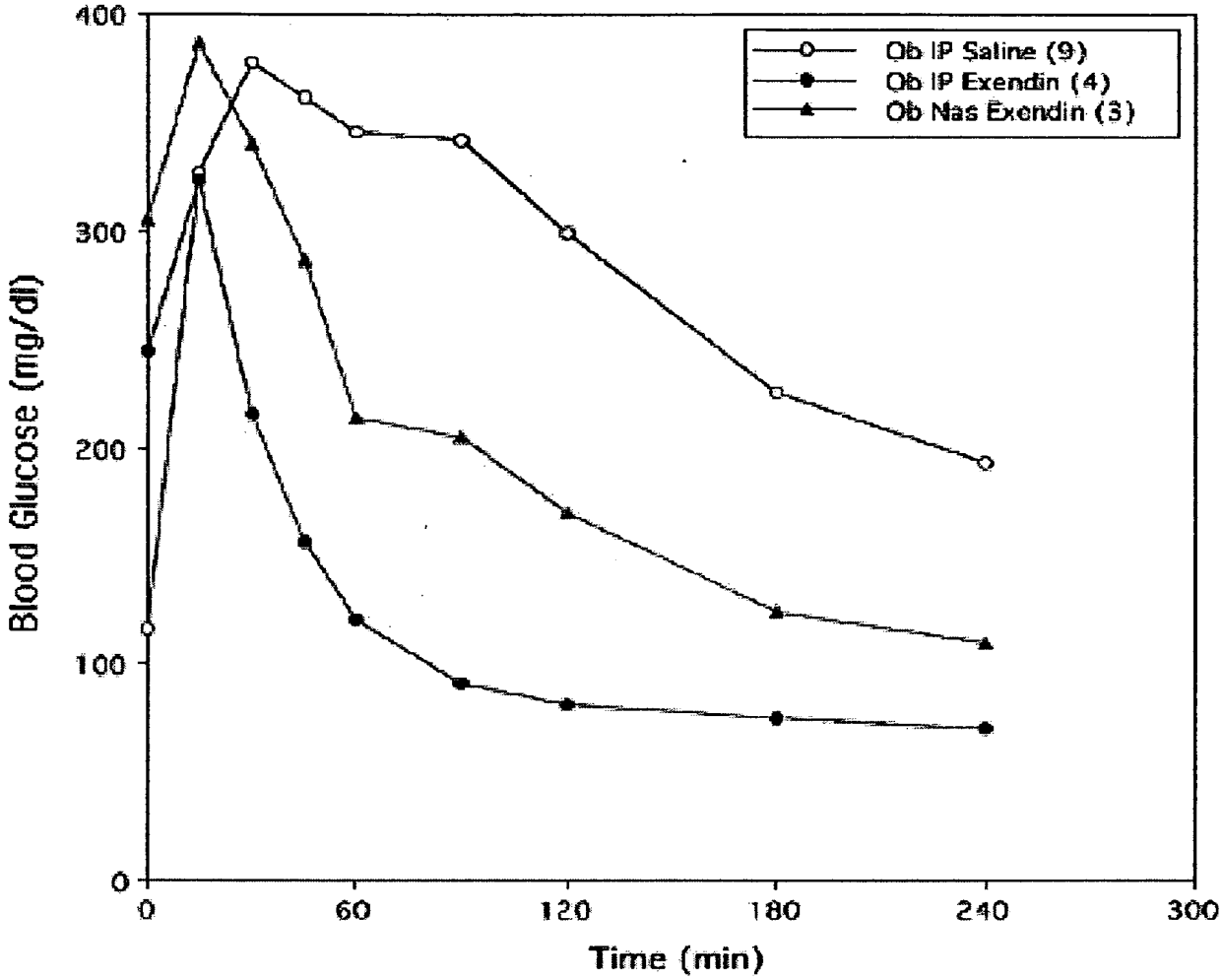


FIG. 3

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APPLICATION DATA SHEET

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APPLICATION INFORMATION

Title Line One::	ABSORPTION ENHANCERS FOR DRUG
Title Line Two::	ADMINISTRATION
Total Drawing Sheets::	Three (3)
Formal Drawings?::	Yes
Application Type::	PROVISIONAL TO UTILITY
Docket Number::	AEGIS1210

CONTINUITY INFORMATION

This application is a ::	Provisional-to-Utility
>Application One::	60/649,958
Filing Date::	February 3, 2005
which is a::	Provisional

Application Two::	60/637,284
Filing Date::	December 17, 2004
which is a::	Provisional
Application Three::	60/632,038
Filing Date::	November 30, 2004
which is a::	Provisional
Application Four::	60/609,890
Filing Date::	September 14, 2004
which is a::	Provisional
Application Five::	60/604,296
Filing Date::	August 25, 2004
which is a::	Provisional

PRIOR FOREIGN APPLICATIONS

Foreign Application One::

Filing Date::

Country::

Priority Claimed::

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ATTORNEY DOCKET NO.:
AEGIS1210

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION**, the specification of which

__X__ is attached hereto.

__X__ was filed on May 11, 2005, (Attorney Docket No.: **AEGIS1210**) as U.S. Application Serial No. _____ and was amended on _____ if applicable (the "Application").

I hereby authorize and request insertion of the application serial number of the Application when officially known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, Code of Federal Regulations ("C.F.R."), § 1.56.

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/649,958	February 3, 2005
(Application Serial No.)	(Filing Date)
60/637,284	December 17, 2004
(Application Serial No.)	(Filing Date)
60/632,038	November 30, 2004
(Application Serial No.)	(Filing Date)
60/609,890	September 14, 2004
(Application Serial No.)	(Filing Date)
60/604,296	August 25, 2004
(Application Serial No.)	(Filing Date)

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of the application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of the Application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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