

08-15-07

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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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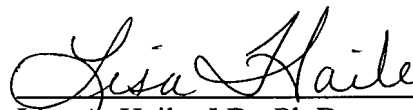
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Check number 586657 in the total amount of \$755.00 is enclosed as payment for the three-month Extension of Time fee (\$225.00), Terminal Disclaimer fee (\$65.00) and Information Disclosure Statement fee (\$180.00). No other fee is deemed necessary 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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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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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 μ L of insulin

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(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 <u>141</u> ± 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:

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OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS GLUCAGON

INSULIN PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

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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.

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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).

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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.

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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).

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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.

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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

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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.

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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.

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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 facie* 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.

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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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