Patent
Attorney Docket No. 0056192-000067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING CONTINUATION / DIVISIONAL APPLICATION UNDER 37 C.F.R. § 1.53(b)

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

Customer Number **21839**

Sir:

☐ **NON-PUBLICATION IS REQUESTED. A CERTIFICATION IS BELOW.**

This is a request for filing a ☒ continuation ☐ divisional application under 37 C.F.R. § 1.53(b) of the following pending application, Application No. 10/551,205, filed November 14, 2006 entitled ORAL FORMULATIONS OF CLADRIBINE

by the following named inventor(s):

Nicholas S. BODOR
Yogesh DANDIKER

☐ The entire disclosure of the prior application from which a copy of the oath or declaration is supplied herewith is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

☐ Applicant(s) hereby requests that the above-captioned application **NOT BE PUBLISHED** under 35 U.S.C. § 122(b) and 37 C.F.R. § 1.211. The undersigned hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen (18) months after filing.

☐ This application is being filed by less than all the inventors named in the prior application. In accordance with 37 C.F.R. § 1.63(d)(2), the Commissioner is requested to delete the name(s) of the following person or persons who are not inventors of the invention being claimed in this application.

☐ This application is being filed by more than all the inventors named in the prior application. In accordance with 37 C.F.R. § 1.63(d)(5), a new oath or declaration is enclosed, and the Commissioner is requested to add the name(s) of the following person or persons who are inventors of the invention being claimed in this application.

☒ Applicant(s) suggests Figure 1 for inclusion on the front page of the patent application publication and patent.

☒ Applicant(s) requests that the published application include the following assignment information: Ares Trading, S.A., Aubonne, Switzerland.

☐ Small entity status is claimed.

1. ☐ Enclosed is a copy of the prior Application No. _____ as originally filed on _____, including copies of the specification, claims, drawings and the executed oath or declaration as filed.

2. ☒ Enclosed is a revised prior application and a copy of the prior executed oath or declaration as filed. No new matter has been added to the revised application.

Buchanan Ingersoll & Rooney PC
Attorneys & Government Relations Professionals

Exhibit
Hopewell EX 1058
02/15/24 - EW
exhibitsticker.com

Hopewell EX1058
Hopewell v. Merck
IPR2023-00481

3. ☒ The filing fee has been calculated as follows ☐ and in accordance with the enclosed Preliminary Amendment:

					FEES
Basic Application Filing Fee (1011)					$ 330
Examination Fee (1311)					220
Search Fee (1111)					540
	No. of Claims		**Extra Claims**	**Rate**	
Total Claims	64	Minus 20=	44	x $ 52 (1202)	2288
Independent Claims	4	Minus 3=	1	x $ 220 (1201)	220
If multiple dependent claims are presented, add 390					$ 0
App. Size Fee (app + dwgs. exceeding 100 sheets) - $270 for each 50 sheets (1081)					$ 0
Total Application Fee					$ 3598
☐ Small Entity Status claimed - subtract 50% of Total Application Fee					0
Add Assignment Recording Fee of $ 40 if Assignment document is enclosed					$ 0
TOTAL APPLICATION FEE DUE					$ 3598

4. ☐ This application is being filed without a filing fee.

5. ☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

6. ☒ Charge $ 3598 to credit card.

7. ☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

8. ☒ New drawings are enclosed.

9. Applicant(s) claims priority under 35 U.S.C. §§ 119 of the following application(s):

Country	Appl. No.	Filing Date MM-DD-YYYY
		MM-DD-YYYY

☐ The certified copy of the priority application:

☐ is enclosed.

☐ was filed on _____ in prior Application No. _____, filed on _____, and acknowledged by the Examiner on _____, in Paper No. _____.

☐ was filed in the International Bureau and acknowledged by the Examiner on _____ in _____.

☐ has not yet been filed.

10. ☐ A Preliminary Amendment is enclosed.

11. ☒ An Information Disclosure Statement, Form Substitute PTO-1449 and (2) documents are enclosed.

12. ☐ A General Authorization of Payment of Fees and Petitions for Extensions of Time is enclosed.

13. ☒ An Application Data Sheet.

14. ☐ Also enclosed is _____.

15. ☒ The power of attorney in the prior application is to Customer Number 21839.

a. ☐ The power appears in the original papers in the prior application.

b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. ☒ Address all future communications to: (may only be completed by applicant, attorney, or agent of record)

Buchanan Ingersoll & Rooney pc
Customer Number **21839**

Date: January 7, 2011

By _____
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

☐ inventor(s)
☐ assignee of complete interest
☒ attorney or agent of record
☐ filed under 37 C.F.R.§ 1.34(a)

APPLICATION DATA SHEET

Application Information

Application Number::	
Filing Date::	January 7, 2011
Application Type::	Regular
Subject Matter::	Utility
Suggested Classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	
Number of CD Disks::	
Number of Copies of CDs::	
Sequence Submission?::	
Computer Readable Form (CRF)?::	
Number of Copies of CRF::	
Title::	ORAL FORMULATIONS OF CLADRIBINE
Attorney Docket Number::	0056192-000067
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	1
Total Drawing Sheets::	1
Small Entity?::	No
Latin Name::	

Variety Denomination Name::	
Petition Included?::	No
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
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Representative Information

Representative Customer Number:: 21839

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation of	10/551,205	November 14, 2006
10/551,205	National Stage of	PCT/US2004/009387	March 26, 2004
PCT/US2004/009387	Claims benefit under 35 U.S.C. §119(e) of	60/458,922	March 28, 2003
PCT/US2004/009387	Claims benefit under 35 U.S.C. §119(e) of	60/484,756	July 2, 2003
PCT/US2004/009387	Claims benefit under 35 U.S.C. §119(e) of	60/541,247	Feb 4, 2004

Foreign Priority Information

Country::	Application Number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee Name::	ARES TRADING S.A.
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Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: January 7, 2011

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

COMBINED DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe 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:

ORAL FORMULATIONS OF CLADRIBINE

the specification of which **(check only one item below)**:

☐ is attached hereto.

☐ was filed as United States Patent application Number _____ on _____ and was amended on _____ (if applicable).

☒ was filed as PCT International application Number PCT/US2004/009387 on March 26, 2004 and was amended on _____ (if applicable).

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 Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §§ 119 (a)-(d), 172 or 365(a) of any foreign application(s) for patent or inventor's certificate or of any international (PCT) application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international (PCT) application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §§119(a)-(d), 172 or 365(a):				
COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (MM/DD/YYYY)	PRIORITY CLAIMED UNDER 35 U.S.C. §§119, 172 OR 365(a)	
			Yes	No

I hereby appoint the attorneys and agents associated with the following PTO Customer Number of Buchanan Ingersoll PC (including attorneys from Burns, Doane, Swecker & Mathis) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and transact all business in connection with international applications directed to said invention:

Customer Number **21839**

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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Date	
Residence (City, State, Country)	
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City, State, ZIP, Country	

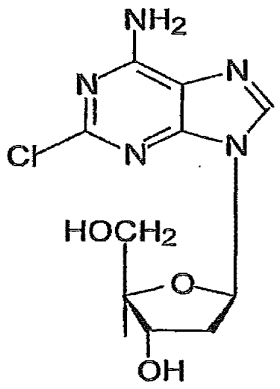
ORAL FORMULATIONS OF CLADRIBINE

CROSS-REFERENCE TO EARLIER APPLICATIONS

This application is a continuation of prior copending US Application No. 10/551,205 filed November 14, 2006, now allowed, which is the US national stage of International Application No. PCT/US2004/009387, filed March 26, 2004, which claims benefit under 35 U.S.C. § 119(e) of United States Provisional Application No. 60/458,922, filed March 28, 2003; of United States Provisional Application No. 60/484,756, filed July 2, 2003; and of United States Provisional Application No. 60/541,247, filed February 4, 2004, all of said applications being hereby incorporated by reference herein in their entireties and relied upon.

BACKGROUND OF THE INVENTION

Cladribine, which is an acid-labile drug, has the chemical structure as set forth below:



It is also known as 2-chloro-2'-deoxyadenosine or 2-CdA. Cladribine exists as a white, nonhydroscopic, crystalline powder, consisting of individual crystals and of crystalline aggregates.

Cladribine is an antimetabolite which has use in the treatment of lymphoproliferative disorders. It has been used to treat experimental leukemias such as L1210 and clinically for hairy cell leukemia and chronic lymphocytic leukemia as well as Waldenstrom's macroglobulinaemia. It has

also been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions including rheumatoid arthritis, inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis) and multiple sclerosis (see *e.g.*, J. Liliemark, *Clin. Parmacokinet*, 32(2): 120-131, 1997). It has also been investigated, either experimentally or clinically in, for example, lymphomas, Langerhan's cell histiocytosis, lupus erythematosus, chronic plaque psoriasis, Sezary syndrome, Bing-Neel syndrome, recurrent glioma, and solid tumors.

Oral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations. Patient compliance is enhanced insofar as oral dosage forms alleviate repeated health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs. At a time of escalating health care costs, the reduced costs associated with oral administration versus parenteral administration costs gain importance. The cost of parenteral administration is much higher due to the requirement that a health care professional administer the cladribine in the health care provider setting, which also includes all attendant costs associated with such administration. Furthermore, in certain instances, therapeutic considerations such as the need for a slow release of cladribine over a prolonged period of time may be practically met only by oral or transmucosal delivery.

However, to date the oral delivery of cladribine has been plagued by low bioavailability (see, *e.g.*, J. Liliemark *et al., J. Clin. Oncol.*, 10(10): 1514-1518, 1992), and suboptimal interpatient variation (see, *e.g.*, J. Liliemark, *Clin. Pharmacokinet*, 32 (2): 120-131, 1997). See also, A. Tarasuik, *et al.* reporting poor absorption and pH dependent lability (*Arch. Immunol. et Therapiae Exper.*, 42: 13-15, 1994).

Cyclodextrins are cyclic oligosaccharides composed of cyclic α-(1→4) linked D-glucopyranose units. Cyclodextrins with six to eight units have

been named α-, β- and γ-cyclodextrin, respectively. The number of units determines the size of the cone-shaped cavity which characterizes cyclodextrins and into which drugs may be included to form stable complexes. A number of derivatives of α-, β- and γ-cyclodextrin are known in which one or more hydroxyl groups is/are replaced with ether groups or other radicals. These compounds are thus known complexing agents and have been previously used in the pharmaceutical field to form inclusion complexes with water-insoluble drugs and to thus solubilize them in aqueous media.

Recently, Schultz *et al.*, in U.S. Patent No. 6,194,395 B1, have described complexing and solubilizing cladribine with cyclodextrin. The Schultz *et al.* patent primarily addresses the problems inherent in previously described aqueous formulations of cladribine, particularly for subcutaneous and intramuscular injection. Schultz *et al.* have found that cladribine is not only significantly more soluble in aqueous media when formulated with cyclodextrin, but also is more stable against acid-catalyzed hydrolysis when combined with cyclodextrin. The latter finding is taught to be of particular benefit in the formulation of solid oral dosage forms, where the compound would normally undergo hydrolysis in the acid pH of the stomach contents. Schultz *et al.* do not appear to have described any actual work in connection with solid oral dosage forms. In fact, they describe only one method of preparing the solid dosage form, which is a melt extrusion process, in which the cladribine and cyclodextrin are mixed with other optional additives and then heated until melting occurs. Furthermore, the broad dosage ranges of 1 mg to 15 mg of cladribine and 100 mg to 500 mg of cyclodextrin listed in the patent suggest no criticality to the particular amount of cyclodextrin to be present with a given amount of cladribine in a solid oral dosage form. Indeed, these dosage ranges include many combinations which may be suitable as mixtures but not for complex formation. For example, a ratio of 1 mg of cladribine to 500 mg of cyclodextrin contains too much cyclodextrin, so

that the drug would not readily leave the complex and achieve its therapeutic function. On the other hand, 15 mg of cladribine and only 100 mg of cyclodextrin would not be enough to complex that amount of cladribine.

The Schultz *et al.* patent does suggest improving the stability of cladribine in oral dosage forms by combining/complexing it with cyclodextrin, but does not suggest improving the drug's oral bioavailability by such means; in fact, the patent does not describe or suggest a method for enhancing or maximizing the bioavailability of cladribine from a solid oral dosage form of cladribine and cyclodextrin, or a composition specially designed to do so.

Many workers have studied the solubility of specific drugs in water containing various concentrations of selected cyclodextrins in order to demonstrate that increasing concentrations of cyclodextrins increase the solubility of the drugs at selected temperatures and pH levels, as for example reported in the Schultz *et al.* patent. Phase solubility studies have also been performed by various workers in order to elucidate the nature of the complex formation, for example, whether the cyclodextrin and drug form a 1:1 complex or a 1:2 complex; see, for example, Harada *et al.* U.S. Patent No. 4,497,803, relating to inclusion complexes of lankacidin-group antibiotics with cyclodextrin, and Shinoda *et al.* U.S. Patent No. 4,478,995, relating to a complex of an acid addition salt of (2'-benzyloxycarbonyl)phenyl trans-4-guanidinomethylcyclohexanecarboxylate with a cyclodextrin.

While Schultz *et al.* teach that a cladribine-cyclodextrin complex improves the water solubility and acid stability of cladribine, the art does not suggest how to maximize or enhance the benefits of the complexation in terms of bioavailability and interpatient variation when the complex is to be administered in a solid oral dosage form.

SUMMARY OF THE INVENTION

It has now been found that amorphous cyclodextrins can be combined with cladribine to form a particularly advantageous product which can be incorporated into a solid oral dosage form. This product is a complex cladribine-cyclodextrin complex, and the solid oral dosage form containing it improves oral bioavailability and/or achieves lower interpatient and/or intrapatient variation of the drug.

The present invention provides a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and a pharmaceutical composition comprising said complex, formulated into a solid oral dosage form. Thus, the cyclodextrin itself is amorphous, the inclusion complex with cladribine is amorphous (and is preferably saturated with cladribine) and the free cladribine which forms the non-inclusion complex is amorphous.

The invention also provides a method for increasing or enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof, a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form which maximizes the amount of cladribine in the inclusion and non-inclusion complexes.

The invention further provides for treatment of conditions responsive to administration of cladribine in mammals by administering thereto the composition of the invention. Use of cladribine in the preparation of the pharmaceutical compositions of the invention for administration to treat

cladribine-responsive conditions and for enhancing the oral bioavailability of cladribine is also provided.

Still further, the invention provides a process for the preparation of a complex cladribine-cyclodextrin complex which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

In yet a further aspect the invention provides a pharmaceutical composition obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

BRIEF DESCRIPTION OF THE DRAWING

A more complete appreciation of the invention and its many attendant advantages will be readily understood by reference to the following detailed description and the accompanying drawing, wherein the sole Figure is a graphical representation of the results of a phase solubility study where various molar concentrations of hydroxypropyl-β-cyclodextrin (HPβCD) are plotted against various cladribine molar concentrations, with (●) representing

the data points obtained for complexation under conditions specified in EXAMPLE 2 below.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the instant specification and claims, the following definitions and general statements are applicable.

The patents, published applications, and scientific literature referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

The term "inclusion complex" as used herein refers to a complex of cladribine with the selected cyclodextrin wherein the hydrophobic portion of the cladribine molecule (the nitrogen-containing ring system) is inserted into the hydrophobic cavity of the cyclodextrin molecule. This is often referred to simply as a cyclodextrin complex of the drug.

The term "non-inclusion complex" refers to a complex which is not an inclusion complex; rather than the hydrophobic portion of cladribine being inserted in the cyclodextrin cavity, the non-inclusion complex is formed primarily by hydrogen-bonding of the hydroxyls and amino group on "free" cladribine, (*i.e.* cladribine not in the inclusion complex) to the hydroxyls on the exterior of the cyclodextrin torus (*e.g.* in the case of hydroxypropyl-β-cyclodextrin, hydroxypropyl and hydroxyl groups on the glucose rings). This is a more loosely-held association than an inclusion complex.

As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a composition, the term "comprising" means that the composition includes at least the recited features or components, but may also include additional features or components.

The terms "consists essentially of" or "consisting essentially of" have a partially closed meaning, that is, they do not permit inclusion of steps or features or components which would substantially change the essential characteristics of a process or composition; for example, steps or features or components which would significantly interfere with the desired properties of the compositions described herein, *i.e.*, the process or composition is limited to the specified steps or materials and those which do not materially affect the basic and novel characteristics of the invention. The basic and novel features herein are the provision of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, so as to provide improved bioavailability and/or lower interpatient and/or intrapatient variation following administration. Essential to the invention is the combination of the amorphous nature of the starting cyclodextrin, and the level of water solubility exhibited by cladribine (about 5 mg/ml at room temperature), and consequently its capability for hydrogen bonding, which can be taken advantage of under particular conditions described hereinafter, and which afford a special amorphous mixture uniquely well-suited for optimizing the oral bioavailability of cladribine.

The terms "consists of" and "consists" are closed terminology and allow only for the inclusion of the recited steps or features or components.

As used herein, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

The term "about" is used herein to means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

The term "amorphous" is used herein to refer to a noncrystalline solid. The cyclodextrins encompassed herein themselves are amorphous because they are each composed of a multitude of individual isomers, and their complexes with cladribine are also amorphous. Further, conditions for complexation can be selected (elevated temperature and prolonged complexation times, as described hereinafter) so that a supersaturated cladribine solution will be formed. When cooled, because of the amorphous nature of the complex and the cyclodextrin, some excess free cladribine does not precipitate but rather is trapped in amorphous form in intimate admixture with the (preferably saturated) amorphous cladribine-cyclodextrin inclusion complex. This excess cladribine forms a loosely-held association, or non-inclusion complex, with the cyclodextrin through hydrogen bonding. This, then, further increases the amount of cladribine in the product; this additional cladribine, because it is amorphous and also because it is in intimate admixture with the amorphous inclusion complex, is expected to be somewhat protected from degradation by stomach acid (although it may not be as protected as the cladribine which is in the form of the inclusion complex).

The term "saturated" when used in conjunction with a complex of cladribine in amorphous cyclodextrin means that the complex is saturated with cladribine, that is, the complex contains the maximum amount of cladribine which can be complexed (by means of both inclusion and non-inclusion complexes) with a given amount of cyclodextrin under the conditions of complexation used. A phase solubility study can be used to provide this information, as described in more detail hereinafter. (Conditions for the complexation are also described in more detail below.) Alternatively, a saturated complex may be arrived at empirically by simply adding cladribine to an aqueous solution of the selected cyclodextrin until no more cladribine goes into solution; ultimately, excess cladribine, if any, is removed (by filtration or centrifugation) and the solution lyophilized to provide the dry saturated complex.

The expression "substantially', as in "substantially free" means within 20% of the exact calculated amount, preferably within 10%, most preferably within 5%.

The term "interpatient variability" refers to variation among patients to which a drug is administered. The term "intrapatient variability" refers to variation experienced by a single patient when dosed at different times.

As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0,

0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

In the specification and claims, the singular forms include plural referents unless the context clearly dictates otherwise. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (2001).

Reference is made hereinafter in detail to specific embodiments of the invention. While the invention will be described in conjunction with these specific embodiments, it will be understood that it is not intended to limit the invention to such specific embodiments. On the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims. In the following description, numerous specific details are set forth in order to provided a thorough understanding of the present invention. The present invention may be practiced without some or all of these specific details. In other instances, well-known process operations have not been described in detail, in order not to unnecessarily obscure the present invention.

There is provided by the present invention compositions, as well as methods of making and of using pharmaceutical compositions, useful to achieve desirable pharmacokinetic properties. Such compositions stem from the discovery that solutions of cyclodextrin and cladribine in which cladribine is in a high thermodynamic state, when presented to the gastric mucosa

through which they are absorbed are associated with improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.

It is postulated, without wishing to so limit the invention, that upon dissolution (*e.g.*, by contact with a fluid, such as a bodily fluid), dry compositions according to the invention form a locally saturated cladribine solution in which cladribine is in the state of highest thermodynamic activity (HTA), thus favoring absorption. Cladribine has a fairly low, although not insignificant, intrinsic aqueous solubility; it is in fact somewhat water soluble. The free cladribine formed from dissociation of the inclusion and non-inclusion complexes in a saturated aqueous solution seeks a more stable activity level by being absorbed through the gastric mucosa.

In view of the foregoing, it is apparent that to produce optimal pharmaceutical compositions, in a solid oral dosage form, these dosage forms should be formulated to release a localized saturated cladribine solution, upon contact of the solid dosage forms with body fluid at the mucosa, in which cladribine is in its HTA state. To provide such a localized saturated solution *in vivo*, it is important to first identify the optimal ratio of cladribine to amorphous cyclodextrin, which ratio is referred to herein as the HTA ratio, to be used in the solid dosage form.

The HTA ratio is empirically determined and is identified as the ratio of cladribine to amorphous cyclodextrin which corresponds to the maximum amount of cladribine that can be complexed with a given amount of the cyclodextrin. The HTA ratio may be determined using an empirical method such as a phase solubility study to determine the saturation concentration of cladribine that can be solubilized with different concentrations of amorphous cyclodextrin solutions. Hence, the method identifies the concentrations at which a saturated cladribine-cyclodextrin complex is formed. It is noted that the molar ratio represented by a point on the phase solubility graph shows

how many moles of amorphous cyclodextrin are the minimum needed to maintain the drug in the complex, under given conditions; this may then be converted to a weight ratio. For example, if a phase solubility diagram shows that 9 moles of a given cyclodextrin are needed to maintain the cladribine in a saturated complex, then multiplying the number of moles of cladribine by its molecular weight and multiplying the number of moles of the selected cyclodextrin by its molecular weight, one can arrive at the ratio of the products as an appropriate optimized weight ratio. A phase solubility study also provides information about the nature of the cladribine-cyclodextrin inclusion complex formed, for example whether the inclusion complex is a 1:1 complex (1 molecule of drug complexed with 1 molecule of cyclodextrin) or a 1:2 complex (1 molecule of drug complexed with 2 molecules of cyclodextrin).

In accordance with the present invention, one can start using either the selected amorphous cyclodextrin, such as hydroxypropyl-β-cyclodextrin (HPβCD) or hydroxypropyl-γ-cyclodextrin, or cladribine as the fixed variable to which an excess of the other is added to identify various solubility data points (indicating saturated cladribine-cyclodextrin complexes) and draw the resultant line. Typically, cladribine is added to an aqueous solution having a known concentration of amorphous cyclextrin under conditions empirically found to promote complex formation. Generally, the complexation is conducted with heating, for example at about 45 to about 60°C for a significant period of time, *e.g.*, at least 6-9 hours; it is believed that even better results can be obtained by heating at up to about 80°C for up to 24 hours. Excess precipitated cladribine is then removed and the cladribine concentration is subsequently measured. This concentration represents the amount of cladribine solubilized for a given amorphous cyclodextrin concentration. This process is repeated for a different known concentration of cyclodextrin until several data points are obtained. Each data point represents the concentration of the cladribine dissolved in a known

concentration of the selected amorphous cyclodextrin. The data points are then plotted to show the concentration of cladribine against the various cyclodextrin concentrations used. The graph is a phase solubility diagram which can be used to determine the amount of cladribine for any specific concentration of cyclodextrin used to form the solution under a given set of complexation conditions. It will be appreciated that the aqueous solubility of cladribine is about 5 mg/ml at room temperature and would be higher at elevated temperature. Consequently, the data points correspond to the amount of cladribine dissolved in aqueous HPβCD or other amorphous cyclodextrin under the selected conditions; when later lyophilized, the solution yields a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex. If equilibrium conditions are reached during the complexation, the amorphous cladribine-cyclodextrin complex will be saturated with cladribine.

One of skill in the art will appreciate that concentrations at which saturated complexes of cladribine with amorphous cyclodextrins are formed (and thus HTA ratios as well) may be identified by a variety of alternative methodologies. Accordingly, any method known in the field suitable to identify these concentrations is within the scope of the invention.

It has been discovered that desirable pharmacological properties (improved bioavailability and/or coefficient of variation as compared to traditional approaches) are associated with mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin.

Using intrinsically amorphous cyclodextrins, for example hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated cyclodextrins, and the like, with cladribine, which is a somewhat water soluble compound (capable of H-bonding through its free hydroxyl and

amino groups), the cladribine provides increased solubility in solutions of these cyclodextrins. Not only is there increased water solubility but also H-bonded association of the cladribine with the cyclodextrin, separately from the actual inclusion complexed material.

One of skill in the art will appreciate that the phase solubility diagram for each given starting concentration ratio represents the starting point of one's investigation on the basis of which variables (reactants' concentrations, temperature and time) may be altered to promote inclusion complex and non-inclusion complex associations favoring a higher or lower proportion of either type of association in the final product. Departure from the ratio of cladribine to cyclodextrin, the temperature and/or the dilution empirically found to promote equilibrium towards complex formation is then analyzed to promote the formation of mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin in various proportions according to the invention.

Thus, for example, by starting with more diluted cyclodextrin (*i.e.*, larger water volumes than that used for solubility plot analysis) logically will accommodate more cladribine in solution sequestering more of the same from complex formation. Upon evaporation, some of the solubilized cladribine will tend to associate with cyclodextrin in a non-inclusion complex fashion. By altering the initial dilution, one may shift equilibrium towards inclusion complex or non-inclusion complex formation. Similarly, by increasing complexation temperature, the water solubility of cladribine may be increased while decreasing the stability of inclusion complexes, thus promoting non-inclusion complexes. Thus, by altering complexation temperature, one may shift equilibrium towards inclusion complex or non-inclusion complex formation. Finally, complexation time may be altered to favor the formation of mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin according to the invention.

As exemplified hereinafter, it is possible to maximize the cladribine in solid amorphous mixtures, by forcing additional cladribine into solution (using more dilute solutions of cyclodextrin, higher temperatures and longer complexation times, as indicated above). When the solution is cooled off, the extensively amorphous nature of these cyclodextrins does not allow crystallization of an excess amount of cladribine beyond that which forms an inclusion complex with the cyclodextrin; and upon freeze-drying/lyophilization, one obtains an amorphous mixture of cladribine-cyclodextrin inclusion complex (which is amorphous) and amorphous free cladribine, loosely associated with uncomplexed cyclodextrin (and even with complexed cyclodextrin) by hydrogen-bonding, that is, the non-inclusion complex.

As shown in the EXAMPLES, this may be done by maximizing solubilization by elevating the temperature (for example, to about 50°to 80°C), and stirring for many hours (up to 24 hours) before freeze-drying. The weight/weight ratios obtained were about 1:14 and 1:11. The apparent optimum weight/weight ratio under these exemplified conditions is the higher of these, or about 1:14 of cladribine: cyclodextrin. If too much excess caldribine is added to the complexation medium, then crystallization of some of the cladribine takes place, which would in turn result in some crystalline cladribine in the product; this undesired excess cladribine is not in solution and is not H-bonded to the amorphous cyclodextrin and lowers the weight ratio. Therefore, it is desirable to carefully control the amount of excess cladribine beyond that which will form the inclusion complex to only the amount which will dissolve in the solution. The desired amorphous mixture of amorphous inclusion complex and amorphous free cladribine can be termed a "complex cladribine-cyclodextrin complex," which includes both inclusion and non-inclusion/H-bonded complexes. The inclusion complex is a complex of cladribine inserted into the hydrophobic cavity of the selected amorphous cyclodextrin, while the non-inclusion/H-bonded complex is

amorphous free cladribine loosely hydrogen-bonded to the cyclodextrin. It is estimated that about two-thirds (60 to 70%) of the cladribine will be in the non-inclusion complex, with the remaining one third (30 to 40%) being in the inclusion complex when the product is obtained as exemplified hereinbelow (17% HPβCD solution, 45 to 50°C complexation temperature for about 9 hours); by increasing the percentage of cyclodextrin used and/or manipulating the temperature, products can be readily obtained in which a much greater proportion of the amorphous mixture is in the form of the inclusion complex. In the case of a representative amorphous cyclodextrin, hydroxypropyl-β-cyclodextrin (HPβCD) a cladribine:cyclodextrin weight ratio of from about 1:10 to about 1:16 is appropriate for the exemplified conditions; the ratio is expected to be the same for hydroxypropyl-γ-cyclodextrin under those conditions. The material obtained is characterized by rapid dissolution of the cladribine in aqueous media.

Freeze-drying, also known as lyophilization, comprises three basic stages: first a freezing stage, then a primary drying stage and finally a secondary drying stage. EXAMPLE 2 below provides details of lyophilization as conducted on the batches described therein. This procedure can be further optimized by following the principles described by Xiaolin (Charlie) Tang and Michael J. Pikal in *Pharmaceutical Research*, Vol. 21, No. 2, February 2004, 191-200, incorporated by reference herein in its entirety and relied upon.

The above-described method requires amorphous cyclodextrins rather than originally crystalline cyclodextrins which have relatively low water solubilities, such as α-, β- or γ-cyclodextrin, 2,6-dimethyl-β-cyclodextrin and the like, because these cyclodextrins would allow crystallization of cladribine in excess of that forming an inclusion complex and therefore would not afford the desired amorphous mixture. The method also would not be useful if cladribine were highly hydrophobic/lipophilic, because in such a situation the drug would not have intrinsic aqueous solubility/H-bonding capability and

could not provide the unique mixture obtained herein. However, in point of fact, cladribine has an aqueous solubility of 5 mg/ml at room temperature, thus a significant amount of the drug will be simply soluble in the water phase especially at higher than room temperature; also, as in the case of HPβCD, for example, some of the cladribine will be associated by hydrogen-bonding to the 2-hydroxypropyl and free glucose-OH groups in the cyclodextrin via the two hydroxy functions found in the deoxyadenosine moiety of the cladribine.

The cyclodextrins within the scope of this invention are amorphous derivatives of the natural cyclodextrins α-, β- or γ-cyclodextrin wherein one or more of the hydroxy groups are substituted, for example, by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy)alkyl groups; and wherein each alkyl or alkylene moiety preferably contains up to six carbons. Although commonly referred to as a single entity, an amorphous cyclodextrin is actually a mixture of many different entities, since the substituent groups can be located on various hydroxyls of the basic cyclodextrin structure. This in turn results in the amorphous nature of these cyclodextrins, which is indeed well-known. Moreover, these cyclodextrins can be obtained in varying degrees of substitution, for example from 1 to 14, preferably from 4 to 7; the degree of substitution is the approximate average number of substituent groups on the cyclodextrin molecule, for example, the approximate number of hydroxypropyl groups in the case of the hydroxpropyl-β-cyclodextrin molecule, and all such variations are within the ambit of this invention. Substituted amorphous cyclodextrins which can be used in the invention include polyethers, for example, as described in U.S. Patent No. 3,459,731. Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl-

C_{1-6}alkyl groups or mixed ethers thereof. In particular, such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxy-C_{2-4}alkyl or carboxy-C_{1-2}alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl. The term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms such as methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like. Other cyclodextrins contemplated for use herein included glucosyl-β-cyclodextrin and maltosyl-β-cyclodextrin. Of particular utility in the present invention are randomly methylated β-cyclodextrin and polyethers such as hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, and hydroxyethyl-γ-cyclodextrin, as well as sulfobutyl ethers, especially β-cyclodextrin sulfobutyl ether. In addition to simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used. Other cyclodextrins are described, for example, in *Chemical and Pharmaceutical Bulletin* 28: 1552-1558 (1980); Yakugyo Jiho No. 6452 (28 March 1983); *Angew. Chem. Int. Ed. Engl.* 19: 344-362 (1980); U.S. Patent Nos. 3,459,731 and 4,535,152; European Patent Nos. EP 0 149 197A and EP 0 197 571A; PCT International Patent Publication No. WO90/12035; and UK Patent Publication GB 2,189,245.

References describing cyclodextrins for use in the compositions according to the present invention, and/or which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: *Cyclodextrin Technology* by Jozsef Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; *Cyclodextrin Chemistry* by M. L. Bender *et al.*, Springer-Verlag, Berlin (1978); *Advances in Carbohydrate Chemistry*, Vol. 12, Ed. By M. L. Wolfrom, Academic Press, New York in the chapter "The Schardinger Dextrins" by Dexter French, pp. 189-260; *Cyclodextrins and their Inclusion Complexes* by J. Szejtli,

Adakemiai Kiado, Budapest, Hungary (1982); I. Tabushi, *Acc. Chem. Research*, 1982, 15, pp. 66-72; W. Sanger, *Angewandte Chemie*, 92, p. 343-361 (1981); A. P. Croft *et al., Tetrahedron*, 39, pp. 1417-1474 (1983); Irie *et al. Pharmaceutical Research*, 5, pp. 713-716 (1988); Pitha *et al., Int. J. Pharm.* 29, 73 (1986); U.S. Patent Nos. 4,659,696 and 4,383,992; German Patent Nos. DE 3,118,218 and DE-3,317,064; and European Patent No. EP 0 094 157A. Patents describing hydroxyalkylated derivative of β- and γ-cyclodextrin include Pitha U.S. Patent Nos. 4,596,795 and 4,727,064, Müller U.S. Patent Nos. 4,764,604 and 4,870,060 and Müller *et al.* U.S. Patent No. 6,407,079.

Amorphous cyclodextrins of particular interest for complexation with cladribine include: hydroxyalkyl, *e.g.* hydroxyethyl or hydroxypropyl, derivatives of β- and γ-cyclodextrin; carboxyalkyl, *e.g.* carboxymethyl or carboxyethyl, derivatives of β- or γ-cyclodextrin; β-cyclodextrin sulfobutyl ether; and randomly methylated β-cyclodextrin. 2-Hydroxypropyl-β-cyclodextrin (HPβCD), 2-hydroxypropyl-γ-cyclodextrin (HPγCD), randomly methylated β-cyclodextrin, β-cyclodextrin sulfobutyl ether, carboxymethyl-β-cyclodextrin (CMβCD) and carboxymethyl-γ-cyclodextrin (CMγCD) are of special interest, especially hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin.

Compositions of an amorphous mixture of amorphous free cladribine and an amorphous, preferably saturated, cladribine-cyclodextrin inclusion complex for use in the present invention can be prepared under conditions favoring complex formation in a liquid environment as described and as exemplified herein. The resultant liquid preparations can be subsequently converted to a dry form suitable for administration as a solid oral or transmucosal dosage form.

One of skill will appreciate that a variety of approaches are available in the field to prepare compositions as described herein. One available

method exemplified herein includes the steps of mixing the cladribine in an aqueous solution of an amorphous cyclodextrin, separating un-dissolved cladribine (*e.g.*, by filtering or centrifugation), and lyophilizing or freeze-drying the saturated solution to form a solid amorphous mixture.

Pharmaceutical compositions according to the invention may optionally include one or more excipients or other pharmaceutically inert components. One of the advantages of the invention, however, is that cladribine drug forms as described herein can be prepared with the minimal amount of excipients necessary for shaping and producing the particular form, such as a tablet or patch. Excipients may be chosen from those that do not interfere with cladribine, with cyclodextrin or with complex formation.

Dosage forms are optionally formulated in a pharmaceutically acceptable vehicle with any of the well-known pharmaceutically acceptable carriers, diluents, binders, lubricants, disintegrants, scavengers, flavoring agents, coloring agents, and excipients (see *Handbook of Pharmaceutical Excipients*, Marcel Dekker Inc., New York and Basel (1998); Lachman *et al.* Eds., *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., (1986); Lieberman *et al.*, Eds. *Pharmaceutical Dosage Forms,* Marcel Dekker Inc., New York and Basel (1989); and *The Handbook of Pharmaceutical Excipients*, 3rd Ed., American Pharmaceutical Association and Pharmaceutical Press, 2000); see also *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA (1990) and *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams & Wilkins, (1995)). A simple solid oral dosage form consists of the amorphous mixture of amorphous free cladribine and amorphous cladribine-cyclodextrin complex (preferably saturated) as described above, *i.e.* the complex cladribine-cyclodextrin complex, compressed with a small amount (*e.g.* about 1% by weight) of a suitable binder or lubricant such as magnesium stearate.

In certain instances, oral absorption may be further facilitated by the addition of various excipients and additives to increase solubility or to enhance penetration, such as by the modification of the microenvirionment.

The methods and pharmaceutical compositions described herein offer novel therapeutic modalities for the treatment of patients in need of treatment with cladribine. As shown herein, the invention addresses the problems of poor bioavailability traditionally associated with oral cladribine.

The compositions of the invention are particularly suitable as modalities for the treatment of any cladribine-responsive disease. Several disease states responsive to cladribine are well-documented in the literature (see *infra*). For any target disease state, an effective amount of the complex cladribine-cyclodextrin comples, *i.e.* the amorphous mixture of the optimized amorphous saturated cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (*e.g.*, an amount affective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

The term "therapeutically effective amount" or "effective amount" is used to denote treatments at dosages effective to achieve the therapeutic result sought. Therapeutically effective dosages described in the literature include those for hairy cell leukemia (0.09 mg/kg/day for 7 days), for multiple sclerosis (from about 0.04 to about 1.0 mg/kg/day (see U.S. Patent No. 5,506,214)); for other diseases, see also U.S. Patent Nos. 5,106,837 (autohemolytic anemia); 5,310,732 (inflammatory bowel disease); 5,401,724 (rheumatoid arthritis); 5,424,296 (malignant astrocytoma); 5,510,336 (histiocytosis); 5,401,724 (chronic myelogenous leukemia); and 6,239,118 (atherosclerosis).

Further, various dosage amounts and dosing regimens have been reported in the literature for use in the treatment of multiple sclerosis; see, for example: Romine et al., *Proceedings of the Association of American*

Physicians, Vol. 111, No. 1, 35-44 (1999); Selby et al., *The Canadian Journal of Neurological Sciences*, 25, 295-299 (1998); Tortorella et al., *Current Opinion in Investigational Drugs*, 2 (12), 1751-1756 (2001); Rice et al., *Neurology,* 54, 1145-1155 (2000); and Karlsson et al., *British Journal of Haematology*, 116, 538-548 (2002); all of which are incorporated by reference herein in their entireties and relied upon.

Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability obtain after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. For further dosing information, see also U.S. Provisional Patent Application No. _____ [IVAX0021-P-USA/Attorney Docket No. 033935-011], and U.S. Provisional Patent Application No. _____ [IVAX0022-P-USA/Attorney Docket No. 033935-012], both entitled "Cladribine Regimen for Treating Multiple Sclerosis", both filed on March 25, 2004 and incorporated by reference herein in their entireties.

Furthermore, one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient. The invention therefore provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal. Therapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.

As noted in the preceding paragraph, administration of cladribine in accord with this invention may be accompanied by administration of one or more additional active ingredients for treating the cladribine-responsive condition. The additional active ingredient will be administered by a route of administration and in dosing amounts and frequencies appropriate for each additional active ingredient and the condition being treated. For example, in the treatment of multiple sclerosis, other useful drugs include interferon beta (Rebif®, Betaseron®/Betaferon®, Avonex®), identical to the naturally occurring protein found in the human body; glatiramer acetate (Copaxone®), a random chain (polymer) of the amino acids glutamic acid, lysine, alanine and tyrosine; natalizumab (Antegren®), a monoclonal antibody; alemtuzumab (Campath-1H®), a humanized anti-CD52 monoclonal antibody; 4-aminopyridine (also known as 4-AP and Fampridine), a drug that blocks the potassium channels in neurons; and amantadine, an anti-viral agent which improves muscle control and reduces muscle stiffness and is used to alleviate the symptoms of fatigue in multiple sclerosis, a purpose for which pemoline (Cylert®) and L-Carnitine (a herbal product) may also be useful. In the treatment of hairy cell leukemia, additional active ingredients may include interferon alpha, pentostatin, fludarabine, rituximab (an anti-CD 20 monoclonal antibody) and the anti-CD22 recombinant immunotoxin BL 22; other additional active ingredients may be appropriate in other types of

leukemias. In the treatment of rheumatoid arthritis, there are many other active ingredients which may be selected. These include NSAIDS (non-steroidal anti-inflammatory drugs), which are of three types: salicylates such as aspirin, traditional NSAIDS such as ibuprofen and indomethacin, and COX-2 inhibitors such as celecoxib (Celebrex®), rofecoxib (Vioxx®), meloxicam (Mobic®), valdecoxib (Bextra®), lumiracoxib (Prexige®) and etoricoxib (Arcoxia®). Other drugs useful in treating rheumatoid arthritis which may be used in conjunction with the present invention include DMARDS, glucocorticoids, biological response modifiers and non-NSAID analgesics. DMARDS are disease-modifying anti-rheumatic drugs which include methotrexate, plaquenil, leflunomide (Arava®), sulfasalazine, gold, penicillamide, cyclosporine, methyl cyclophosamide and azathioprine. Glucocorticoids include dexamethasone, prednisolone, triamcinolone and many others. Biological response modifiers (which restore the disease-fighting ability of the immune system), include etanercept (Enrel®), a tumor-necrosis factor inhibitor, infliximab (Remicade®), which is also an anti-TNF drug, anakinra (Kineret®), a selective IL-1 blocker, and Humira®, a human monoclonal antibody which is another anti-TNF drug. The non-NSAID analgesics include acetaminophen as well as narcotic analgesics such as hydrocodone, oxycodone and propoxyphene. Generally speaking, those drugs which work by a mechanism different from that of cladribine are particularly useful for concomitant therapy with the cladribine composition described herein. Those drugs which are effective by the oral route of administration and which are compatible with the instant cladribine complexes in a single dosage form may be incorporated into the instant dosage forms; otherwise, they should of course be separately administered in amounts, frequencies and via administration routes suitable to them.

As used herein, "treating" means reducing, preventing, hindering the development of, controlling, alleviating and/or reversing the symptoms in the individual to which a compound of the invention has been administered, as

compared to the symptoms of an individual not being treated according to the invention. A practitioner will appreciate that the complexes, compositions, dosage forms and methods described herein are to be used in concomitance with continuous clinical evaluations by a skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

The methods of the present invention are intended for use with any subject/patient that may experience the benefits of the methods of the invention. Thus, in accordance with the invention, the terms "subjects" as well as "patients" include humans as well as non-human subjects, particularly domesticated animals.

Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein.

EXAMPLES

EXAMPLE 1

PHASE SOLUBILITY STUDY

A phase solubility study can be carried out as follows. Excess cladribine is added to cyclodextrin solutions of various concentrations of

hydroxypropyl-β-cyclodextrin (HPβCD) and allowed to complex as described in EXAMPLE 2 below. The excess, undissolved cladribine is removed by filtration. The amount of cladribine in the complexation solution is measured to obtain a data point. This process is repeated with different known concentrations of HPβCD until several data points are obtained. These data points are then plotted graphically, each data point representing the amount of cladribine that can be dissolved in water with a specific concentration of cyclodextrin. Points on the line generated by the data points represent ratios for the product. One of skill in the art will realize the same results will be generated if excess cyclodextrin is added to cladribine solutions of known concentration.

The molar concentrations of cladribine to cyclodextrin obtained are plotted and presented graphically. A representative phase solubility diagram is shown in the Figure. The plotted lines for cladribine-HPβCD represent cladribine solubilization for the conditions tested, that is, the ratio of the concentration of cladribine to the concentration of cyclodextrin. The area above each of the plotted lines represents conditions where excess insoluble cladribine is present. The area below each of the plotted lines represents the conditions where cyclodextrin is in excess.

The plot for cladribine-HPβCD shown in the Figure is approximately linear; this is indicative of a 1:1 complex, in which one molecule of the drug is complexed with one molecule of cyclodextrin. The Figure also shows that additional cyclodextrin is needed to maintain the cladribine in the complex. For example, about 0.14 mole of HPβCD is needed to maintain about 0.049 mole of cladribine dissolved under the selected conditions, which will ultimately provide the amorphous mixture of the amorphous, preferably saturated, cladribine-HPβCD inclusion complex and amorphous free cladribine (as a non-inclusion complex). Under the conditions of EXAMPLE 2 below, a significant portion of the cladribine in the product can be expected to be not in the inclusion complex but rather in amorphous form loosely held

in intimate admixture therewith by hydrogen bonding as a non-inclusion complex.

EXAMPLE 2

PREPARATION OF CLADRIBINE-CYCLODEXTRIN COMPLEX FOR HUMAN TRIALS

Cladribine is complexed with HPβCD by the following method.

In 825 mL of distilled water, 172.5 g of hydroxypropyl-β-cyclodextrin are dissolved (forming an approximately 17% solution), then cladribine is added and the mixture is stirred at about 45 to about 50°C for about nine hours. Stirring is continued for an additional 6 to 9 hours at room temperature. Any undissolved cladribine is removed by filtration and the solution is cooled to room temperature. To form the amorphous mixture of amorphous cladribine-cyclodextrin complex and amorphous free cladribine, the aqueous cladribine-cyclodextrin solution is dried by lyophilization prior to incorporation into solid oral tablets. The lyophilization procedure comprises a freezing stage of rapidly bringing the complexation solution to about -40°C to about -80°C (e.g., about -45°C) for approximately 2 to 4 hours (preferably about 3 to 4 hours), followed by a primary drying stage at about -25°C for approximately 80-90 hours, typically under low pressure, and a second drying stage at about 30°C for about 15-20 hours.

Product made by the foregoing general procedure can be analyzed by HPLC (utilizing a Hypersil ODS 3 micron column and an acetonitrile based mobile phase, with UV detection at 264 nm) to find the weight ratio of cladribine to cyclodextrin in the final product. Final product preparations can be further characterized by methods known in the art, including, for example by inspecting appearance, ascertaining the overall impurity content by HPLC, ascertaining the water content using a Karl Fischer titrator, determining the dissolution profile by a standard method, for example using USP<711>Apparatus II equipment and UV detection at 264 nm, inspecting

the content uniformity and performing quantitative assay by HPLC analysis of the active ingredient.

Two batches of cladribine/cyclodextrin product, FD04 and FD05, were made by the foregoing general procedure as follows:

Purified water (825 mL) was pre-heated at 48°C (target range 45°C to 50°C) in a 1-liter glass vessel by immersion in a water bath. The heated water was stirred to achieve a controlled central vortex. 2-hydroxypropyl-β-cyclodextrin (172.50 g) was weighed and slowly added to the heated water over a period of 40 minutes. The resulting solution was stirred for a further 10 minutes to ensure complete dissolution of the cyclodextrin. Cladribine (12.00 g for FD04 and 18.75 g for FD05) was weighed and added to the stirred cyclodextrin solution, which turned cloudy before becoming clear. The resulting clear solution was maintained at 48°C and continually stirred for 9 hours. Stirring continued for a further 7 hours while the solution cooled to room temperature.

Use of a larger amount of cladribine in the preparation of FD05 was part of an attempt to optimize the procedure; however, it was found that the initial amount of cladribine in that case was too great and precipitation was observed at the end of the cooling step for batch FD05. The solution was filtered to remove the precipitate. Analysis of the resultant product revealed (assay value = 87.2%) that 16.35 g of cladribine had been incorporated into the cyclodextrin complex in the case of FD05. No filtration was required for batch FD04, indicating that the amounts used in the preparation of FD04 were more appropriate and that the FD05 procedure could be optimized by beginning with a smaller amount of cladribine (16.35 g rather than 18.75 g), thus avoiding the filtration step.

After cooling to room temperature and, in the case of FD05, filtering, the solutions were filled into 100 mL lyophilization vials (20 mL solutions per vial), the filled vials were partially stoppered and lyophilized. The

lyophilization included freezing at -45°C for about 200 minutes, a primary drying phase at -25°C under a pressure of 100 mTorr for about 5,200 minutes and a secondary drying phase at 30°C for about 1,080 minutes as set forth below:

TABLE I

Step	Process	Temperature	Pressure (mTorr)	Time (min)
1	Load	4°C		
2	Load Hold	4°C	n/a	120
3	Ramp	-45°C	n/a	120
4	Freezing	-45°C	n/a	200
5	Ramp	-25°C	100	120
6	Primary drying	-25°C	100	5200
7	Ramp	30°C	50	240
8	Secondary drying	30°C	50	1080
9	Finish	30°C	Vials closed under vacuum	

The FD04 and FD05 batches of cladribine/cyclodextrin product made by the foregoing procedure were analyzed by HPLC (utilizing a Hypersil ODS 3 micron column and an acetonitrile based mobile phase with UV detection at 264 nm) and empirically found to have the following characteristics:

TABLE II

Lot No.	Cladribine: HPβCD w/w	Cladribine: HPβCD Weight Ratio
FD04	12.00g:172.50g	1:14.38
FD05	16.35g:172.50g	1:10.55

The products were analyzed by DSC thermograms and X-ray diffraction methods to determine any free crystalline cladribine in the lyophilized material. Importantly, the samples exhibited no transitions in the region of 210°C to 230°C, which is associated with the melting of crystalline cladribine. In both cases, no significant thermal activity was recorded in the range of 210°C to 230°C, suggesting that the complexes obtained at the end of the lyophilization do not have any significant amount of free crystalline cladribine, considering the sensitivity of the analytical method (up to 3% w/w). This conclusion was supported by the absence of peaks for crystalline cladribine from X-ray diffraction traces for both complexes FD04 and FD05.

The products are amorphous mixtures of amorphous cladribine-HPβCD inclusion complex and amorphous free cladribine hydrogen-bonded to the cyclodextrin as a non-inclusion complex. The cladribine:HPβCD weight ratios obtained were about 1:14 and 1:11.

Generally speaking, amorphous mixtures within the scope of the present invention have cladribine:HPβCD weight ratios of from about 1:10 to 1:16.

EXAMPLE 3

PREPARATION OF ORAL TABLETS

Tablets were manufactured using batches of amorphous mixtures FD04 and FD05 described in EXAMPLE 2 for use in a clinical study.

Batch N0120 was manufactured using cladribine-2-HPβCD complex mixture DF05 to a batch size of 3,000 tablets and batch N0126 was manufactured using cladribine-HPβCD complex mixture FD04 to a batch size of 800 tablets. The master formulations for the two batches are shown in TABLE III. Batch N0120 represented 3.0 g tablets and Batch N0126 represented 10 mg tablets for clinical study.

TABLE III

Constituent	Lot Number	mg/tablet 3.0 mg Batch N0120	mg/tablet 10.0 mg Batch N0126
Cladribine-HPβCD complex mix	FD05	30.60*	
Cladribine-HPβCD complex mix	FD04		153.75**
Sorbitol powder NF	1007403	68.4	44.25
Magnesium stearate NF	1006280	1.00	2.00
Total		100.00	200.00

*Equivalent to 3.0 mg cladribine per tablet.
**Equivalent to 10.0 mg cladribine per tablet.

The following table sets forth the method of manufacture of the Batch N0120 and N0126 tablets.

TABLE IV

1.	Pre-mix the magnesium stearate with an approximately equal quantity of sorbitol power.
2.	Pass the cladribine-HPβCD complex and the remainder of the sorbitol powder into a one-liter glass jar via a 40-mesh screen.
3.	Blend the contents for 10 minutes at 12 rpm.
4.	Pass the magnesium stearate/sorbitol powder pre-mix into the glass jar via the 40-mesh screen.
5.	Blend the final mixture for 5 minutes at 12 rpm.
6.	Compress into 3.0 mg and 10.0 mg tablets at a target compression weight of 100 mg and 200 mg, respectively.

Both the Batch N0120 3.0 mg tablets and the Batch N0126 10.0 mg tablets were round, with one side flat-beveled edged and the other side shallow convex. The Batch N0120 3.0 mg tablets had an average weight of 100 mg, a thickness of 2.7 mm, a friability of 0.2%, a hardness of 4 Kp and a disintegration time of 3 minutes. The Batch N0126 10.0 mg tablets had an average weight of 198 mg, a thickness of 4.2 mm, a friability of 1%, a hardness of 2.8 Kp and a disintegration time of 5 minutes 42 seconds.

The Batch N0120 3.0 mg and N0126 10.0 mg tablets were used in the clinical study summarized in EXAMPLE 5 below.

EXAMPLE 4

CLINICAL STUDY: RELATIVE BIOAVAILABILITY

The objective of this study was to assess the relative bioavailability of three oral cladribine formulations: (1) a cyclodextrin-based formulation according to the instant invention (Tablet 1: complex FD05, i.e. Batch No. N0120 tablets described above); (2) a mucoadhesive formulation (Tablet 2: containing 3.0 mg cladribine, 10 mg of Carbopol 71G NF, 22.2 mg of dicalcium phosphate, 64.3 mg of lactose and 0.5 mg of magnesium stearate, Batch No. N0121); and (3) a hard-gel capsule (Capsule containing 3.0 mg cladribine, 5.0 mg Carbopol 974P, 91.3 mg Avicel PH101, 100.0 mg Avicel PH102, 0.2 mg colloidal silicon dioxide and 0.5 mg magnesium stearate, Batch No. RD03030) in comparison with one fixed subcutaneous clardribine administration (reference formulation) in patients with MS (multiple sclerosis).

This study was a 2 center, open-label, randomized, 4-way crossover single dose study using twelve patients with MS. Patients received randomly three different fixed oral doses (3.0 mg) and a fixed subcutaneous dose of 3.0 mg. The four treatment days were separated by a drug-free interval of at

least 5 days. In each treatment period, blood samples were collected over a 24-hour period for evaluation of plasma cladribine.

The plasma concentration of cladribine was measured by a HPLC/MS/MS method. Using this method, the relationship between concentration versus peak area ratio was found to be linear within the range of 100 pg/ml to 50,000 pg/ml for cladribine. The limit of quantification was 100 pg/ml. Analysis of samples was carried out in 16 runs. No calibrator had to be excluded from fitting of the calibration curve and accuracy of each quality control sample met the GLP requirements.

576 clinical plasma samples were analyzed and concentration values of cladribine were determined. The results were compiled and are summarized in the tables below (Tables V and VI). In these tables, the following definitions are applicable: T_{max} is the time to reach maximum concentration in the plasma; $T_{½}$ is the half-life of cladribine in the plasma; C_{MAX} is the maximum concentration of cladribine in the plasma; AUC_{inf} is the area under the curve for the measured data from zero extrapolated to infinity; AUC_t is the area under the curve for the measured data (from zero to the last time point); Geom Mean is the geometric mean; CV is the coefficient of variation (relative standard deviation); LL is the lower limit; UL is the upper limit.

TABLE V
Summary Statistics for Pharmacokinetic Parameters for Cladribine Study
Obtained via Non-Compartmental Analyses. (n=12).

Pharmacokinetic Parameter	3.0 mg subcutaneous			3mg Tablet 1			3mg Tablet 2			3 mg Capsule		
	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)
T_{max}(hr)	N/A	.313 ±.113	36.2	N/A	.521 ±.167	32.1	N/A	1.25 ±.839	67.1	N/A	2.25 ±.622	27.7
$T_{½}$(hr)	N/A	6.69 ±2.01	30.1	N/A	7.55 ±2.50	33.1	N/A	6.73 ±2.82	41.9	N/A	6.27 ±2.31	36.9
C_{max}(pg/ml)	23186	N/A	40.1	6597	N/A	24.7	5041	N/A	52.6	3818	N/A	36.8
AUC_{inf} (hr·pg/ml)	57254	N/A	44.4	24936	N/A	28.8	21676	N/A	42.7	22604	N/A	39.5
AUC_t (hr·pg/ml)	54725	N/A	43.8	23182	N/A	28.0	20063	N/A	42.1	20951	N/A	42.0

**CV=SD/mean for T_{max} and $T_{½}$ and CV% geometric mean for C_{max}, AUC_{inf} and AUC_t.

TABLE VI

Ratios of Oral to Subcutaneous Pharmacokinetic Parameters and Corresponding Two-Sided 90% Confidence Intervals for Cladribine Study (n=12).

Pharmacokinetic Parameter	3 mg Tablet 1		3mg Tablet 2		3mg Capsule	
	Ratio*	LL, UL	Ratio*	LL, UL	Ratio*	LL, UL
AUC_{inf}	43.1	35.7, 52.1	38.4	31.8, 46.4	38.9	32.1, 47.0
AUC_t	41.9	34.6, 50.8	37.2	30.7, 45.0	37.6	31.0, 45.5

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

EXAMPLE 5

CLINICAL STUDY: DOSE RESPONSE AND ABSOLUTE BIOAVAILABILITY

The objective of this study was to assess the systemic availability of cladribine after oral administration in two different fixed oral doses, in comparison with one fixed intravenous administration (reference formulation) in patients with MS (multiple sclerosis), and to evaluate the safety and tolerability of cladribine in this population.

This study was a 3 center, open-label, randomized, 3-way crossover single dose study using twenty-six patients with MS. Patients received randomly two different fixed oral doses (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg (administered as a 1 hour infusion). The three treatment days were separated by a drug-free interval of at least 5 days. In

each treatment period blood samples were collected over a 24-hour period for evaluation of plasma cladribine.

The plasma concentrations of cladribine were measured by a HPLC/MS/MS method. Using this method the relationship between concentrations versus peak area ratios was found to be linear within the range of 100 pg/ml to 50,000 pg/ml for cladribine. The limit of quantification was 100 pg/ml. Analysis of samples was carried out in 16 runs. Except the first run (which had to be rejected because of equipment failure), all other runs could be accepted. No calibrator had to be excluded from fitting of the calibration curve and accuracy of each quality control sample met the GLP requirements.

858 clinical plasma samples were analyzed and concentration values of cladribine were determined. The results were compiled and are summarized in the tables below [TABLES VII through X]. In these tables, the following definitions are applicable: T_{max} is the time to reach maximum concentration in the plasma; $T_{1/2}$ is the half-life of cladribine in the plasma; C_{max} is the maximum concentration of cladribine in the plasma; AUC_{inf} is the area under the curve for the measured data from zero extrapolated to infinity; AUC_t is the area under the curve for the measured data (from zero to the last time point); Geom Mean is the geometric mean; CV is the coefficient of variation (relative standard deviation); LL is the lower limit; UL is the upper limit; σ^2 is the mean variance; σ_B^2 is the mean variance between subjects; σ_W^2 is the mean variance within subjects; CV_T is the total coefficient of variation; and CV_W is the coefficient of variation within subjects.

TABLE VII

Summary Statistics for Pharmacokinetic Parameters for Cladribine Study Obtained via Non-Compartmental Analysis (n=26)

Pharmaco-kinetic Parameter	3.0 mg IV infusion			Oral Administration					
				3.0 mg			10.0 mg		
	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)
T_{max}(hr)	N/A	.817 ±.397	48.6	N/A	.548 ±.300	54.8	N/A	.558 ±.204	36.5
$T_{½}$(hr)	N/A	6.50 ±1.27	19.5	N/A	5.85 ±1.18	20.2	N/A	5.60 ±0.75	13.3
C_{max}(pg/ml)	21425	N/A	27.6	5608	N/A	49.5	21242	N/A	50.5
AUC_{inf} (hr·pg/ml)	58528	N/A	24.0	20159	N/A	35.0	76690	N/A	30.3
AUC_t (hr·pg/ml)	56396	N/A	24.0	19166	N/A	36.9	74532	N/A	30.3

**CV=SD/mean for T_{max} and $T_{½}$ and CV% geometric mean for C_{max}, AUC_{inf} and AUC_t.

TABLE VIII

Ratios of Oral to I.V. Pharmacokinetic Parameters and Corresponding Lower Limit (LL) for the one-sided 95% Confidence Interval for Cladribine Study (n=26)

Pharmacokinetic Parameter	Oral Administration			
	3.0 mg		10.0 mg	
	Ratio*	LL	Ratio*	LL
AUC_{inf}	34.5	31.7	39.1	35.9
AUC_t	34.0	31.2	39.4	36.1

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

TABLE IX

Ratios and Corresponding two-sided 90% Confidence Intervals for Cladribine Study (n=26)

Pharmacokinetic Parameter	10.0 mg/3.0 mg		
	Ratio*	LL	UL
C_{max}	112.6	95.1	133.3
AUC_{inf}	113.3	104.2	123.3
AUC_t	115.8	106.1	126.5

*Ratios (dose normalized) and Corresponding 90% CI obtained via inverse transformation of log-transformed data.

TABLE X

Variance components for Cladribine Study (n=26)

Source of variation	C_{max}	AUC_{inf}	AUC_t
Between (σ_B^2)	.0380	.0487	.0492
With (σ_W^2)	.1315	.0330	.0357
TOTAL ($\sigma_B^2 + \sigma_W^2$)	.1695	.0816	.0849
CV_T(%)	43.0	29.2	29.8
CV_W(%)	37.5	18.3	19.1

Where PK parameters are dose-adjusted and $CV = \sqrt{\exp(\sigma^2) - 1}$

The foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents thereof may be resorted to, falling within the scope of the invention claimed.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.

3. The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

5. The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

6. The composition according to Claim 5, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

7. The composition according to Claim 1, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

8. The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

9. A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

10. The method according to Claim 9, wherein the complex is saturated with cladribine.

11. The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

12. The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

13. The method according to Claim 9, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

14. The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

15. The method according to Claim 9, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve

of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

16. The method according to Claim 9, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

17. A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

18. The method according to Claim 17, wherein the complex is saturated with cladribine.

19. The method according to Claim 17, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

20. The method according to Claim 19, wherein the cladribine-responsive condition is multiple sclerosis.

21. The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

22. The method according to Claim 17, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

23. The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

24. The method according to Claim 17, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

26. The complex according to Claim 25, saturated with cladribine.

27. The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

28. The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

29. The complex according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

30. The complex according to Claim 29, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

31. The complex according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

32. A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 25, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

33. The process according to Claim 32, further comprising a filtration step following step (ii).

34. The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

35. The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

36. The process according to Claim 34, wherein step (i) is performed with stirring.

37. The process according to Claim 36, wherein step (i) is performed for a period of from about 6 to about 9 hours.

38. The process according to Claim 32, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

39. The process according to Claim 32, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

40. The process according to Claim 39, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

41. The process according to Claim 34, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i), or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

42. The process according to Claim 41, wherein 825 parts by volume of water are introduced in step (i).

43. The process according to Claim 32, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

44. The process according to Claim 43, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

45. The process according to Claim 43, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

46. A pharmaceutical composition according to Claim 1, obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

47. The pharmaceutical composition according to Claim 46, wherein the process further comprises a filtration step following step (i) or (ii).

48. The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

49. The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

50. The pharmaceutical composition according to Claim 48, wherein step (i) of the process is performed with stirring.

51. The pharmaceutical composition according to Claim 50, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

52. The pharmaceutical composition according to Claim 46, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

53. The pharmaceutical composition according Claim 46, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

54. The pharmaceutical composition according to Claim 53, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

55. The pharmaceutical composition according to Claim 48, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

56. The pharmaceutical composition according to Claim 55, wherein 825 parts by volume of water are introduced in step (i) of the process.

57. The pharmaceutical composition according to Claim 46, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

58. The pharmaceutical composition according to Claim 57, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

59. The pharmaceutical composition according to Claim 57, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

60. The pharmaceutical composition according to Claim 46, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

61. The pharmaceutical composition according to Claim 60, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

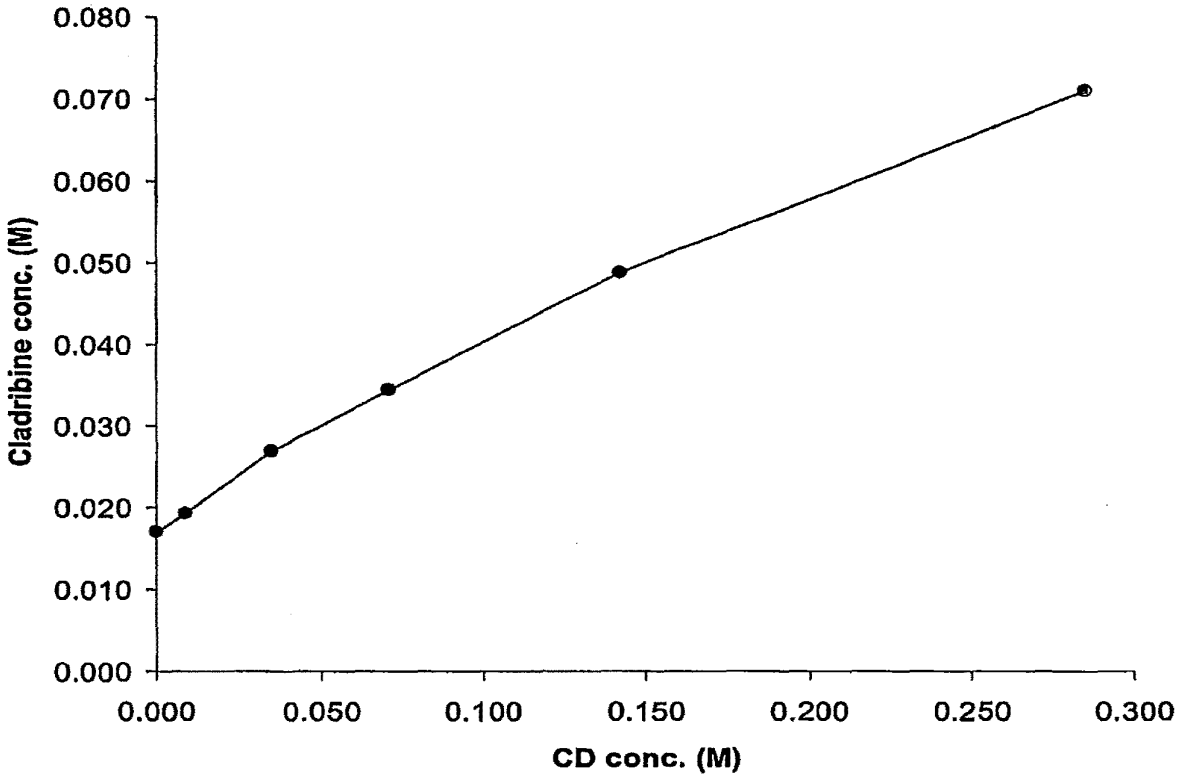
62. The method according to Claim 17, wherein the administration of cladribine is accompanied by administration of one or more additional active ingredients for treating the cladribine-responsive condition.

63. The method according to Claim 62, wherein the cladribine-responsive condition is multiple sclerosis.

64. The method according to Claim 63, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatirimer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

ABSTRACT

Provided are compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine..


0.080
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
Cladribine conc. (M)
0.000
0.050
0.100
0.150
0.200
0.250
0.300
CD conc. (M)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	)	Group Art Unit:
Application No.:	)	Examiner:
Filed: January 5, 2011	)	Confirmation No.:
For: ORAL FORMULATIONS OF CLADRIBINE	)	Continuation of Application No. 10/551,205, filed November 14, 2006, now allowed

FIRST INFORMATION DISCLOSURE STATEMENT

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

Sir:

In accordance with the duty of disclosure as set forth in 37 C.F.R. § 1.56, the accompanying information is being submitted in accordance with 37 C.F.R. §§ 1.97 and 1.98. Applicants request the Examiner's consideration of the documents listed on the accompanying substitute Form PTO-1449.

All of the listed documents were previously made of record in prior Application No. 10/551,205, filed November 14, 2006, upon which Applicants rely for the benefits provided in 35 U.S.C. § 120. In accordance with 37 C.F.R. § 1.98, a copy of each of the listed documents, is not required. For the Examiner's convenience, however, further copies of the International Search Report (ISR) and International Preliminary Report on Patentability and Written Opinion issued during the international phase of the parent application are provided herewith.

This Statement, substitute Form PTO-1449 and other documents are being submitted within three (3) months of the filing or entry of the national stage of this application or before the first Office Action on the merits, whichever is later. Since these documents are being filed within the time period set forth in 37 C.F.R. § 1.97(b), no fee or statement is required.

The following remarks are offered with respect to the listed documents which are not in English:

DE 31 18 218 is in German. Applicants do not have an English translation. However, an English abstract was provided in the parent; the abstract and the citation of the

document in the instant specification serve as a brief statement of relevance. Applicants consider this a general state of the art reference.

DE 33 17 064 is in German. Applicants do not have an English translation but provided an English abstract in the parent. The abstract and citation of the document in the specification serve as a brief statement of relevance. Applicants consider this a general state of the art reference.

EP 0 194 197 B1 is in German, although the claims are also present in English and a full English translation was provided in parent Application No. 10/551,205, filed November 14, 2006. This document is cited in the specification and applicants consider it to be a general state of the art reference.

The non-patent literature document by Shen GAO was cited during prosecution of the corresponding Chinese application and is in the Chinese language. An English translation of the cited section (page 105, lines 25-29) was filed in the parent application. This reference was cited as relevant only to some of the process and product-by-process claims.

The Van Axel Castelli et al. article and the three non-patent literature documents listed immediately after it are not prior art. They were submitted during prosecution of the parent to support positions taken by applicants therein.

It is respectfully requested that an Examiner-initialed copy of the enclosed Substitute Form PTO-1449 be returned to the undersigned.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: January 7, 2011

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known

Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-4,383,992	05-17-1983	Lipari	
	US-6,239,118 B1	05-29-2001	Shatz et al.	
	US-5,424,296	06-13-1995	Saven et al.	
	US-5,510,336	04-23-1996	Saven et al.	
	US-5,506,214	04-09-1996	Beutler	
	US-4,659,696	04-21-1987	Hirai et al.	
	US-3,459,731	08-05-1969	Gramera et al.	
	US-4,478,995	10-23-1984	Shinoda et al.	
	US-5,310,732	05-10-1994	Carson et al.	
	US-5,401,724	03-28-1995	Beutler	
	US-5,106,837	04-21-1992	Carson et al.	
	US-4,497,803	02-05-1985	Harada et al.	
	US-6,194,395 B1	02-27-2001	Schultz et al.	
	US-6,407,079 B1	06-18-2002	Müller et al.	
	US-4,870,060	09-26-1989	Müller	
	US-4,727,064	02-23-1988	Pitha	
	US-4,596,795	06-24-1986	Pitha	
	US-4,764,604	08-16-1988	Müller	
	US-4,535,152	08-13-1985	Szejtli et al.	
	US-6,174,873	01-16-2001	Wrenn, Jr. et al.	
	US-6,699,849	03-02-2004	Loftsson et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	
	EP 0 197 571 A2	10-15-1986	Janssen Pharmaceutica N.V.							X	
	WO 90/12035A1	10-18-1990	Janssen Pharmaceutica N.V.							X	
	DE 31 18 218 A1	04-22-1982	Chinoin Gyogyszer Es Vegyeszet						X	X	
	DE 33 17 064 A1	11-15-1984	Consortium Elektrochem Ind						X	X	
	GB 2 189 245 A	10-21-1987	American Maize-Products Company							X	
	EP 0 149 197 B1	07-24-1985	Janssen Pharmaceutica N.V.	X						X	
	EP 0 094 157 A1	11-16-1983	Janssen Pharmaceutica N.V.							X	
	WO 99/42111	08-26-1999	Cyclops, ehf								

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known

Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

FOREIGN PATENT DOCUMENTS

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	TARASIUK et al., "Stability of 2-Chloro-2'-Deoxyadenosine at Various pH and Temperature", *Archivum Immunologiae et Therapiae Experimentalis*, Vol. 42, pp. 13-15, 1994, published by Birkhauser Publishers Ltd., Basel, Switzerland
	ROMINE et al., "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis", *Proceedings of the Association of American Physicians*, Vol. 111, No. 1, pp. 35-44, 1999, published by Blackwell Publishing, Malden, MA
	TORTORELLA et al., *Current Opinion on Investigational Drugs*, 2(12), pp. 1751-1756, 2001, published by PharmaPress Ltd., London, GB
	SELBY et al., "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis", *Can. J. Neurol Sci.*, Vol. 25, pp. 295-299, 1998, published by Canadian Journal of Neurological Science, Calgary, Canada
	RICE et al., "Cladribine and progressive MS Clinical and MRI outcomes of a multicenter controlled trial", *Neurology*, Vol. 54, pp. 1145-1155, 2000, published by Lippincott Williams and Wilkins, Hagerstown, MD
	LILIEMARK et al., "On the Bioavailability of Oral and Subcutaneous 2-Chloro-2'-Deoxyadenosine in Humans: Alternative Routes of Administration", *Journal of Clinical Oncology*, Vol. 10, No. 10, pp. 1514-1518, 1992, published by American Society of Clinicial Oncology, Alexandria, VA
	KARLSSON et al., "Oral cladribine for B-cell chronic lymphocytic leukaemia: report of a phase II trial with a 3-d, 3-weekly schedule in untreated and pretreated patients, and a long-term follow-up of 126 previously untreated patients", *British Journal of Haematology*, Vol. 116, pp. 538-548, 2002, published by Blackwell Science Ltd., Oxford, UK
	LILIEMARK, "The Clinical Pharmacokinetics of Cladribine" *Clin. Pharmacokinet*, Vol. 32 (2), pp. 120-131, 1997, published by Adis International Limited, Wolters Kluwer Health, Yardley, PA
	NAKAI et al., "Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose V: Comparison with Tri-O-methyl-β-cyclodextrin Ground Mixtures", *Chem. Pharm. Bulletin*, Vol. 28(5), pp. 1552-1558, 1980, published by Pharmaceutical Society of Japan, Tokyo, Japan
	SAENGER, "Clyclodextrin Inclusion Compounds in Research and Industry", *Angew. Chem. Int. Ed. Engl.*, Vol. 19, pp. 344-362, 1980, published by Verlag Chemie, GmbH, Weinheim, Germany
	TANG et al., "Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice", *Pharmaceutical Research*, Vol. 21, No. 2, pp. 191-200, 2004, Springer, The Netherlands
	GAO, Shen, *New Dosage Form and New Technology of Modern Drugs*, first edition, January 2002, Chapter 6, Section 3 (III) Procedures, page 105, lines 25-29 (published by People's Military Medical Publisher) and English translation thereof
	ALBERTIONI et al., "On the bioavailability of 2-chloro-2'-deoxyadenosine (CdA)", *Eur J Clin Pharmacol.*, Vol. 44, pp. 579-582, 1993, Springer-Verlag, Germany
	AHN et al., "Chiral Recognition in Gas-Phase Cyclodextrin: Amino Acid Complexes-Is the Three Point Interaction Still Valid in the Gas Phase?", *J Am Soc Mass Spectrom*, Vol. 12, pp. 278-287, 2001, Elsevier Science, Inc., US

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 3 of 4

Complete if Known

Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	BAKTHIAR et al., "A study of the complexation between dimethyl-β-cyclodextrin and steroid hormones using electrospray ionization mass spectrometry", *Rapid Communications in Mass Spectrometry*, Vol. 11, pp. 1478-1481, 1997, John Wiley And Sons Ltd, England
	BEUTLER et al., "The treatment of chronic progressive multiple sclerosis with cladribine", *Proc. Natl. Acad. Sci. USA, Medical Sciences*, Vol. 93, pp. 1716-1720, 1996, National Academy of Sciences, US
	CHENG et al., "Measurement of chiral complexes of cyclodextrin and amino acids by electrospray ionization time-of-flight mass spectrometry", *J. Mass Spectrom*, Vol. 36, pp. 834-836, 2001, John Wiley & Sons, Ltd., England
	CHOI et al., "FT-Raman and FT-IR Spectra of the Non-steroidal Anti-inflammatory Drug Ketoprofen Included in Cyclodextrins", *Analytical Sciences*, Vol. 17 Supplement, pp. i785-i788, 2001, The Japan Society for Analytical Chemistry, Japan
	GIORDANO et al., "Thermal analysis of cyclodextrins and their inclusion compounds", *Thermochimica Acta 380*, pp. 123-151, 2001, Elsevier Science B.V., The Netherlands
	HWANG et al., "Water Suppression That Works. Excitation Sculpting Using Arbitrary Waveforms and Pulsed Field Gradients", *Journal of Magnetic Resonance*, Series A, Vol. 112, pp. 275-279, 1995, Academic Press, Inc., US
	LAMCHARFI et al., "Electrospray Ionization Mass Spectrometry in Supramolecular Chemistry: Characterization of Non-covalent Cyclodextrin Complexes", *Journal of Mass Spectrometry*, Vol. 31, pp. 982-986, 1996, John Wiley & Sons, Ltd., England
	LOFTSSON et al., "Pharmaceutical Applications of Cyclodextrin. 1. Drug Solubilization and Stabilization", *Journal of Pharmaceutical Sciences*, Vol. 85, No. 10, pp. 1017-1025, 1996, American Pharmaceutical Association and the American Chemical Society, US
	MEIER et al., "The Influence of β- and γ-Cyclodextrin Cavity Size on the Association Constant with Decanoate and Octanoate Anions", *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, Vol. 40, pp. 291-295, 2001, Kluwer Academic Publishers, The Netherlands
	MURA et al., "Interactions of ketoprofen and ibuprofen with β-cyclodextrins in solution and in the solid state", *International Journal of Pharmaceutics*, Vol. 166, pp. 189-203, 1998, Elsevier Science B.V., The Netherlands
	NOLAN et al., "Preparation of Vesicles and Nanoparticles of Amphiphilic Cyclodextrins Containing Labile Disulfide Bonds", *Langmuir*, Vol. 19, pp. 4469-4472, 2003, American Chemical Society, US
	RAMANATHAN et al., "Electrospray Ionization Mass Spectrometric Study of Encapsulation of Amino Acids by Cyclodextrins", J. *Am Soc Mass Spectrom*, Vol. 6, pp. 866-871, 1995, American Society for Mass Spectrometry, US
	REDENTI et al., "Raman and Solid State ^{13}C-NMR Investigation of the Structure of the 1 : 1 Amorphous Piroxicam : β-Cyclodextrin Inclusion Compound", *Biospectroscopy*, Vol. 5, pp. 243-251, 1999, John Wiley & Sons, Inc., US
	SIPE et al., "Cladribine in treatment of chronic progressive multiple sclerosis", *The Lancet*, Vol. 344, pp. 9-13, 1994, Lancet Publishing Group, England
	SZEJTLI, "Introduction and General Overview of Cyclodextrin Chemistry", *Chem. Rev.*, Vol. 98, pp. 1743-1753, 1998, American Chemical Society, US
	UEKAMA et al., "Cyclodextrin Drug Carrier Systems", *Chem. Rev.*, Vol. 98, pp. 2045-2076, 1998, American Chemical Society, US

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 4 of 4

Complete if Known

Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

	UEKAMA et al., "Peracylated β-Cyclodextrins as Novel Sustained-release Carriers for a Water-soluble Drug, Molsidomine", *J. Pharm. Pharmacol.*, Vol. 46, pp. 714-717, 1994, Pharmaceutical Press, England
	TADDEI et al., "Influence of Environment on Piroxicam Polymorphism: Vibrational Spectroscopic Study", *Biopolymers (Biospectroscopy)*, Vol. 62, pp. 68-78, 2001, John Wiley & Sons, Inc., US
	VAN AXEL CASTELLI et al. "Characterisation of an Inclusion Complex Between Cladribine and 2-Hydroxypropyl-β-Cyclodextrin," *J. Pharm.Sci.*, Vol. 97, No. 9, September 2008, pp. 3897-3906, Wiley InterScience and the American Pharmacists Association, US
	Drugs.com, "Oral Investigational Treatment Cladribine Tablets for Multiple Sclerosis Significantly Reduced Relapse Rate in Phase III Pivotal Trial," accessed online February 3, 2009, at http://www.drugs.com/clinical_trials/oral-investigational-cladribine-multiple-sclerosis
	"Serono's Oral Cladribine for the Treatment of Multiple Sclerosis Awarded Fast Track Status by FDA", accessed online February 3, 2009 at http://prnewswire.com
	Merck Serono News Release, "Two-year Phase III Data Presented at AAN 61st Annual Meeting Show Positive Outcome of Cladribine Tablets in Patients with Multiple Sclerosis", April 29/30, 2009, available online.
	LOFTSSON et al., "Self-Association and Cyclodextrin Solubilization of Drugs", *Journal of Pharmaceutical Sciences,* 2002, 91(11), p.2307-2316
	Entry for Liquid, Britannica Online Encyclopedia, http://www.search.eb.com/, accessed online December 31, 2008
	SUZUKI, et al., "Application of Freezing Point Depression to Drug Interaction Studies,"*Chem. Pharm. Bull.,* 1988 36(2), p. 720-725
	SUZUKI et al., "A Study of 1:1 Plus 1:2 Complexes Between Barbiturate and α-Cyclodextrin Using the Freezing Point Depression Method," *Chem. Pharm. Bull.,* 1993, 41(8), P1444-1447

	OTHER
	International Search Report dated October 12, 2004 for PCT/US2004/009387, filed March 26, 2004
	PCT International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2004/009387, International Filing date March 26, 2004.

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 033935-008	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/009387	International filing date *(day/month/year)* 26 March 2004 (26.03.2004)	Priority date *(day/month/year)* 28 March 2003 (28.03.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A61K 9/20, 47/48, 31/52		
Applicant IVAX CORPORATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 October 2005 (01.10.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Beate Giffo-Schmitt Telephone No. +41 22 338 87 20

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT 08 DEC 2004
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/009387	26.03.2004	28.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/20, A61K47/48, A61K31/52

Applicant
IVAX CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Toulacis, C

Telephone No. +49 89 2399-8638

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13-35 with regard to industrial applicability

because:

☒ the said international application, or the said claims Nos. 13-35 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-98
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-98
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12, 36-98
	No:	Claims	

2. Citations and explanations

see separate sheet

III

Claims 13-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V

For the assessment of the present claims 13-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

(N) A cladribine-cyclodextrin complex which is an intimate amorphous admixture of: a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and b) amorphous cyclodextrin as non-inclusion complex (claim 58), is not disclosed in the documents cited in the search report.
The same applies to a pharmaceutical composition comprising said cladribine-cyclodextrin complex (claim 1), to a method for enhancing the oral bioavailability of cladribine comprising oral administration of said complex (claim 13), to a method for the treatment according to claim 25 comprising oral administration of said complex, to the use of said cladribine-cyclodextrin complex in the formulation of a solid oral dosage form (claims 36 and 47), to a process for the preparation of said complex (claim 67), and to a pharmaceutical composition being obtainable by a process according to claim 67 (claim 82).

(IS) The object of the present application is to provide an oral pharmaceutical composition showing improved bioavailability of cladribine and interpatient variation, when administered orally (description, page 4, lines 22-26).
This object has been achieved, by formulating a cladribine-cyclodextrin complex as defined in claim 58, i.e. is an intimate amorphous admixture of a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and b) amorphous cyclodextrin as non-inclusion complex, into a solid oral dosage form (description; page 33, example 4; page 35, table V; page 36, table VI; example 5, tables VII-X).

This is not suggested by document US-B-6 194 395 (D1), which only discloses as an oral dosage form of cladribine, a milled extrudate comprising 1-15 mg cladribine and 100-500 mg cyclodextrin without giving an exact ratio and being silent about amorphous forms (D1; column 6).

(IA) The industrial applicability of claims 1-12 and 36-98 is beyond any doubt.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000067

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	44	52	2288
Independent claims in excess of 3	1201	1	220	220
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3598**

Electronic Acknowledgement Receipt

EFS ID:	9185944
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000067
Receipt Date:	07-JAN-2011
Filing Date:	
Time Stamp:	12:04:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$3598
RAM confirmation Number	8455
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	005619267CONT.pdf	133899 e438bb52501012f29b045a477b3efeffe2aa558a	no	3
Warnings:					
Information:					
2	Application Data Sheet	005619267ADS.pdf	88641 ea0a99e13dfd34b94162b58b685036fdddf13651	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	005619267OATH.pdf	111313 6e6ec35099ae80048f419e65d7c1dedb9e1e8b28	no	2
Warnings:					
Information:					
4		005619267SPEC.pdf	2317450 b918c36a641c6bb697d87a46324b8504a49a7ce4	yes	50

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	39
Claims	40	48
Abstract	49	49
Drawings-only black and white line drawings	50	50

Warnings:					
Information:					
5	Transmittal Letter	005619267IDS.pdf	96019 232d03e9e7060296247acc14bf16f65ed1f9bb8b	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Filed (SB/08)	005619267Fm1449.pdf	392829 809abd94cf3f8b7eaee47c5f0ab2a00b2b8a03da	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					

7	NPL Documents	ISR.pdf	207941 81029896f5be8b1100daff0eaf5736ee548f6737	no	5
Warnings:					
Information:					
8	NPL Documents	IPER.pdf	330298 1fa6f0a8993f9e0fd7dfcf443a7b08193a7abfac	no	8
Warnings:					
Information:					
9	Fee Worksheet (PTO-875)	fee-info.pdf	37904 1812dad1b520c49f2a8ee5b13cf43b78a1d51b63	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3716294		

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 APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/986,310

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	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	64 minus 20 =	* 44			OR	x 52 =	2288
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 220 =	220
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	3598

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	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	

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	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 found in the appropriate box in column 1.

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/986,310	01/07/2011	1623	3598	0056192-000067	64	4

CONFIRMATION NO. 6100

21839
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

FILING RECEIPT

OC000000045534863

Date Mailed: 01/20/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Nicholas S. Bodor, Bal Harbour, FL;
Yogesh Dandiker, Toronto, CANADA;

Assignment For Published Patent Application

ARES TRADING S.A., Aubonne, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 21839

Domestic Priority data as claimed by applicant

This application is a CON of 10/551,205 11/14/2006
which is a 371 of PCT/US2004/009387 03/26/2004
which claims benefit of 60/458,922 03/28/2003
and claims benefit of 60/484,756 07/02/2003
and claims benefit of 60/541,247 02/04/2004

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 01/18/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/986,310**

Projected Publication Date: 04/28/2011

Non-Publication Request: No

Early Publication Request: No

Title

ORAL FORMULATIONS OF CLADRIBINE

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/986,310	01/07/2011	Nicholas S. Bodor	0056192-000067

CONFIRMATION NO. 6100

21839
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

PUBLICATION NOTICE



Title:ORAL FORMULATIONS OF CLADRIBINE

Publication No.US-2011-0097306-A1
Publication Date:04/28/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 13974

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 13974

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

ARES TRADING S.A.
ZONE INDUSTRIELLE D L'OURIETTAZ
CH-1170 AUBONNE, SWITZERLAND

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Kahrs Von Ballmoos	Date 10.04.2012
Name	Bjoern Colin KAHRS	Telephone
Title	~~Authorized Representative~~ Prisca VON BALLMOOS Authorized Representative	

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Ares Trading S.A.

Application No./Patent No.: 12/986,310 Filed/Issue Date: 01/07/2011

Titled: ORAL FORMULATIONS OF CLADRIBINE

Ares Trading S.A. , a CORPORATION

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Nicholas S. Bodor; Yogesh Dandiker To: Ivax Corporation

The document was recorded in the United States Patent and Trademark Office at
Reel 018337 , Frame 0636, or for which a copy thereof is attached.

2. From: Ivax Corporation To: Ares Trading S.A.

The document was recorded in the United States Patent and Trademark Office at
Reel 018337 , Frame 0696, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Mary Katherine Baumeister/ JULY 30, 2012

Signature Date

Mary Katherine Baumeister, Reg. No. 26254 Agent for Applicant(s)

Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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 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.**

Electronic Acknowledgement Receipt

EFS ID:	13371700
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Martin A. Bruehs/Louie Malloy
Filer Authorized By:	Martin A. Bruehs
Attorney Docket Number:	0056192-000067
Receipt Date:	30-JUL-2012
Filing Date:	07-JAN-2011
Time Stamp:	15:17:32
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	Power of Attorney	AresTradingSA.pdf	72559 6fb92021a1041a66c651e9a9487e28c97684de7b	no	1

Warnings:	
Information:	**87**

2	Assignee showing of ownership per 37 CFR 3.73(b).	0056192-0067.pdf	30069 3d732cb3cdfcc2c4058981d4bf267b0451e28d0f	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	102628

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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.

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/986,310	01/07/2011	Nicholas S. Bodor	0056192-000067

CONFIRMATION NO. 6100

13974
SNR DENTON US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

POA ACCEPTANCE LETTER

OC000000055766837

Date Mailed: 08/07/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/30/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/snguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/986,310	01/07/2011	Nicholas S. Bodor	0056192-000067

CONFIRMATION NO. 6100

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(Not for submission under 37 CFR 1.99)

Application Number	12986310
Filing Date	2011-01-07
First Named Inventor	Nicholas S. BODOR
Art Unit	1623
Examiner Name	Jonathan S. LAU
Attorney Docket Number	20009904-0067

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	1	99/62958	WO	A1	1999-12-09	Janssen Pharmaceutica N.V.	Corresponds to JP 2002-517521	☐
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Drugs in Japan (Nihon Iyakuhinn Shu), 2004 edition, JIHOU Inc. March 1, 2003, pp. 651-654, "Cladrivine" (especially, "Composition") - relevance explained in January 10, 2012, Japanese Official Action	☐
	2	Official Action issued on January 10, 2012, in corresponding Japanese Patent Application No. 2006-509371, and an English language translation of the Official Action.	☒

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Bibliographic data: WO9962958 (A1) — 1999-12-09

ACYLATED ALKYLATED CYCLODEXTRIN DERIVATIVES AND THEIR USE AS CARRIERS FOR MEDICAMENTS

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Classification:	**- international:** ***A61K47/48; C08B37/16;*** (IPC1-7): A61K47/48; C08B37/16 **- European:** A61K47/48W18B; B82Y5/00; C08B37/00M2B
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Abstract of WO9962958 (A1)

Cyclodextrin derivatives having at least one lower alkyl group and at least one C2-20 alkanoyl group in the molecule, are disclosed pharmaceutical preparations wherein the derivative and a medicament are in such a state that they are closely compounded, are also disclosed. The cyclodextrin derivative having lowered hemolytic activity and its use as a medicament carrier.

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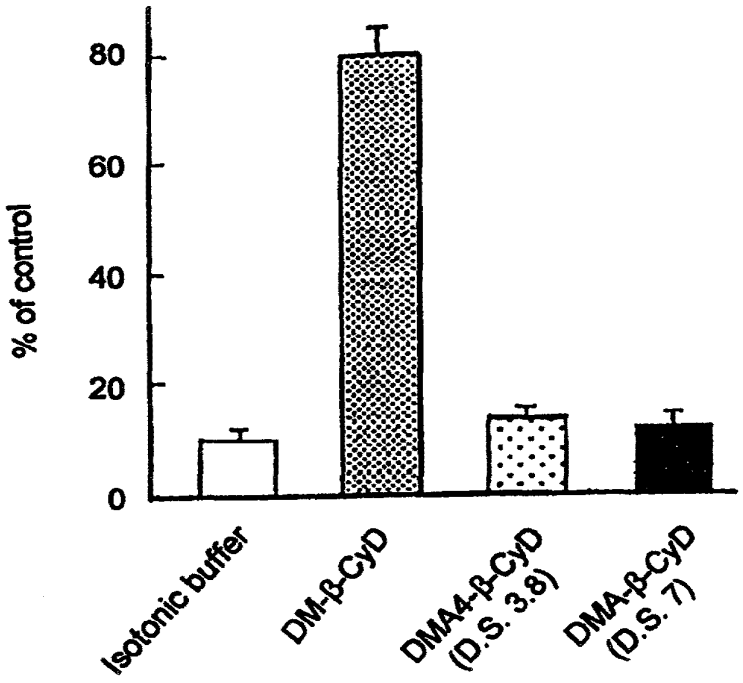
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(54) Title: ACYLATED ALKYLATED CYCLODEXTRIN DERIVATIVES AND THEIR USE AS CARRIERS FOR MEDICAMENTS

(57) Abstract

Cyclodextrin derivatives having at least one lower alkyl group and at least one C_{2-20} alkanoyl group in the molecule, are disclosed pharmaceutical preparations wherein the derivative and a medicament are in such a state that they are closely compounded, are also disclosed. The cyclodextrin derivative having lowered hemolytic activity and its use as a medicament carrier.



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DESCRIPTION

ACYLATED ALKYLATED CYCLODEXTRIN DERIVATIVES AND THEIR USE AS CARRIERS FOR MEDICAMENTS

Technical Field

This invention relates to acylated alkylated cyclodextrin derivatives, and a process for preparing the same and use of the same as carriers for medicaments.

Background Art

Cyclodextrin (hereinafter also referred to as CyD) is an oligosaccharide wherein glucose residues are cyclicly bound by α-1,4 bond and composed of 6, 7 or 8 glucose residues, and ones called α, β or γ-CyD are known. Further, so-called branched cyclodextrins (hereinafter also referred to as branched CyD) are also known wherein glucosyl group(s) or maltosyl group(s) is/are α-1,6 bound to one or two of the glucose units of these CyDs.

These CyDs and branched CyDs have high inclusion ability on certain chemical substances, and are utilized for various uses such as stabilization of unstable substances, retention of volatile substances and solubilization of water-sparingly soluble or insoluble substances, in the pharmaceutical, food and cosmetic fields.

Further, in order to utilize the physicochemical characteristics and inclusion ability of the above CyDs as polyfunctional medicament carriers, etc., various CyD derivatives are provided. However, in the course of these researches, the presence of several problems in physical properties, inclusion ability, intracorporeal kinetics, economical efficiency, etc. has been pointed out, and it has come to be made clear that

there is some limitation on their use. Particularly, use thereof as medicament carriers, namely dissolution aids (solubilizers) or tissular disorder-preventing agents for injections or various preparations to be applied to the mucosae (e.g., eye drops, suppositories, etc.), on which low hemolytic activity, low actions to give topical irritation and low actions to cause tissular disorder are required, has been extremely inconvenient.

On the other hand, α-CyD has a solubility in water as comparatively high as 14.5 g/100 mL (25℃) and its hemolytic activity and muscular irritation are lower than those of β-CyD, but there is a limitation on α-CyD that the guest compounds of inclusion are limited to small molecules. Further, its price is 30 times as high as that of β-CyD and it has a disadvantage point also in an economical aspect. γ-CyD is the best among α-, β- and γ-CyD on the aspect of safety such as hemolytic activity and actions to cause tissular disorder and has inclusion ability equal to that of β-CyD, but its price is about 100 times as high as that of β-CyD and therefore it has not so been utilized from economical reason. Further, glucosylated or maltosylated branched CyDs rouse interest partially because their solubilities in water are increased compared with the corresponding unbranched CyDs, but they are not always satisfactory in behavior as carriers for the above medicaments.

Thus, attempts have been made to improve the physical properties or functionality of β-CyD, which is easy to obtain, by chemically modifying it. For example, there have been obtained thereby heptakis (2,6-di-O-methyl)-β-CyD (hereinafter referred to as DM-β-CyD) wherein the hydroxyl groups at the 2- and 6-positions of the glucose are methylated, heptakis (2,3,6-tri-O-methyl)-β-CyD (hereinafter referred to as TM-β-CyD) wherein all the hydroxyl groups at the 2-, 3- and

6-positions of the glucose are methylated, 2-hydroxypropyl-β-CyD (hereinafter referred to as HP-β-CyD) wherein a hydroxypropyl group is introduced in the hydroxyl group mainly at the 6-position of the glucose, etc. Szejtili et al. suggest that it is possible to utilize DM-β-CyD as a dissolution aid for injection (J. Incl. Phenom., 1(2), 135 (1983)).

However, this DM-β-CyD is extremely easy to dissolve in water and has strong inclusion ability, but has a problem that since its solubility and stability constant strikinly decrease at the side of high temperatures and the dissociation of the medicament from the medicament inclusion composite becomes easy, the designation of sterilization conditions for the injection is hindered. Moreover, DM-β-CyD has a stronger hemolytic activity than β-CyD, and its action to cause tissular disorder at the time of intramusclular injection is also larger than β-CyD. This tendency is the same in TM-β-CyD, and TM-β-CyD shows intermediate values between DM-β-CyD and β-CyD. On the other hand, as to HP-β-CyD, large improvement is made on the lowering of solubility and the lowering of stability constant at high temperatures, and actions to cause tissular disorder such as hemolytic activity and muscular irritation are also considerably improved compared with β-CyD, but they are equal to those of α-CyD, and it is the state of things that HP-β-CyD is far inferior to γ-CyD which has the lowest hemolytic activity and muscular irritation among natural CyDs.

Uwagama et al. disclose a pharmaceutical preparation wherein 2-hydroxyethyl-CyD (hereinafter referred to as HE-β-CyD) wherein a 2-hydroxyethyl group is introduced or 2,3-dihydroxypropyl-CyD (hereinafter referred to as DHP-β-CyD) is used as a carrier for medicaments utilizing its low hemolytic activity or action to inhibit hemolytic activity, low action to

cause tissular disorder or action to prevent tissular disorder, low action to give topical irritation or action to lower topical irritation (Japanese Laid-open Patent Publication No. 61430/1989). However, the hemolysis-inhibiting action of HE-β-CyD and DHP-β-CyD is almost equal to that of γ-CyD, and further improvement will be desired to provide them for clinical use.

Szejtili et al. propose (carboxy)alkyloxyalkyl derivatives of CyD and a pharmaceutical composition comprising such a derivative and a medicament (WO92/14762). However, there is no specific description on whether they show a sufficient hemolytic activity-inhibiting action or not.

Disclosure of Invention

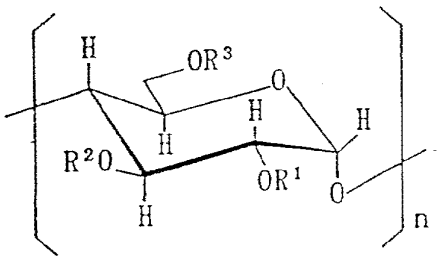
Under such a situation, it becomes very important to provide a low hemolytic medicament carrier. Namely, this is because if a low hemolytic medicament carrier, which makes it possible to administer sparingly soluble medicaments parenterally, can be provided, it can be expected, also for such a medicament that it has been thought to be impossible to apply it, to maintain its high concentration in the blood, and it is thought to make great contribution to the field of pharmacotherapy. Therefore, the objects of the invention lie in providing CyD derivatives satisfying the above needs, and providing the actual use of such a CyD derivative as a carrier or delivery tool for sparingly soluble medicaments.

For solving the above problems, the present inventors have synthesized various CyD derivatives, and examined their hemolysis-inhibiting action. As a result, they found that CyDs having an acyl group and an alkyl group together in the molecule are CyD derivatives having a hemolytic activity that is significantly lower even compared with HE-β-CyD and γ-CyD whose hemolytic

activities have hitherto been recognized to be low. It was further recognized that these derivatives sufficiently retain the medicament inclusion ability of the corresponding CyDs.

Therefore, according to the invention are provided acylated alkylated CyDs useful as solubilizers, adsorbents or agents having inclusion ability.

The acylated alkylated CyD according to the invention is, specifically, an acylated alkylated cyclodextrin derivative represented by the formula (I)



(I)

wherein n is any of integers 6, 7 and 8, and the 1-position and the 4-position of the sugar residues at the both ends are mutually bound by a covalent bond,

R^1, R^2 and R^3 independently represent hydrogen atoms, lower alkyl groups or C_{2-20} alkanoyl groups, or in some case, represent glucosyl groups or maltosyl groups whose hydroxyl group(s) may be replaced with lower alkyloxy group(s) or C_{2-20} alkanyloxy group(s),

provided that any of R^1, R^2 and R^3 of the number of total $3 \times n$ composed of each n are simultaneously at least one lower alkyl group and at least one acyl group, and the residual groups, when exist, are hydrogen atoms or the glucosyl groups or maltosyl groups of the number of up to at most 2.

There is a case where such derivatives are

provided as compounds wherein the degree of substitution of the acyl group and/or alkyl group is different or part thereof are epimerized, depending on starting materials, reaction conditions, etc. for preparing them, or there is also a case where it is convenient to provide them as a form of a mixture. Moreover, the acylated alkylated CyD derivatives sufficiently meet the objects of the invention, even in the form of mixtures, and thus such mixtures are also provided by the invention.

The acylated alkylated CyD derivatives or mixtures of two or more of the derivatives can efficiently be prepared by acylation reaction using corresponding partially alkylated CyD derivatives as starting materials. Thus, such a process for preparing an acylated alkylated CyD is also provided by the invention.

The acylated alkylated CyD derivatives or mixtures of two or more of the derivatives, even if they are derived from β-CyD, not only show hemolytic activities significantly lower compared with HE-β-CyD and γ-CyD which have been recognized to have low hemolytic activity, but sufficiently retain the inclusion ability on medicaments which parent β-CyD inherently has. Moreover, rabbit muscular irritation of the acylated alkylated CyD derivatives is much weaker than that of DM-β-CyD.

Thus, according to the invention is provided the above acylated alkylated CyD derivatives or use of the derivatives as carriers or delivery tools for water soluble, sparingly water soluble or water insoluble medicaments. As a specific embodiment of this use is provided a pharmaceutical preparation which comprises such an acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives and such a medicament in such a state that they are closely compounded. A process for preparing such a pharmaceutical

preparation is also provided.

Brief Description of Drawings

Fig. 1 is the mass spectrum (matrix: methanol, glycerol and m-nitrobenzyl alcohol, which is the same hereinafter) of DMA-β-CyD obtained in Example 1.

Fig. 2 is the ^{1}H-NMR spectrum of DMA-β-CyD obtained in Example 1.

Fig. 3 is the ^{1}H-NMR spectrum of DMA4-β-CyD obtained in Example 2.

Fig. 4 is the ^{1}H-NMR spectrum of butyrated DM-β-CyD obtained in Example 3.

Fig. 5 is the ^{1}H-NMR spectrum of octanoylated DM-β-CyD obtained in Example 4.

Fig. 6 is a drawing showing the results of the hemolytic activity test on various CyD derivatives. In figure 6, the white square (□), black triangle (▲), white triangle (△), white circle (○), black circle (●), white inverted triangle (▽), and white diamond (◇) represent DMA-β-CyD, DMA4-β-CyD, β-CyD, DM-β-CyD, TM-β-CyD, 2-HP-β-CyD with a degree of substitution (D.S.) of 4.8 and sulfobutyl ether β-CyD with a D.S. of 3.5, respectively.

Fig. 7 is a graph showing the released amounts of cholesterol from the intact erythrocytes at the time when various CyD derivatives are contacted with erythrocytes. The vertical axis represents the released amount (%) of cholesterol supposing that the amount of cholesterol in all the erythrocytes is 100 %.

Detailed Description of the Invention

The "acylated alkylated" in the invention means such a state that an acyl group and an alkyl group exist simultaneously on one molecule. Therefore, in the acylated alkylated CyD derivative in the invention, at least one of the hydroxyl groups in the CyD molecule is

converted to an acyl ester, and at least one of the other hydroxyl groups is converted to an alkyl ether.

Surprisingly, such a CyD derivative which simultaneously has an acyl group and an alkyl group on the CyD molecule has a significantly lower hemolytic activity than the corresponding CyD, as stated above. However, in view of significantly lowering hemolytic activity, in the above formula (I), is preferred a CyD derivative wherein 50 % (e.g, 7 as to β-CyD) or more of R^1 and R^3 of the number of total 2×n (e.g, 14 as to β-CyD) are lower alkyl groups, the residual R^1 and R^3 and R^2 are at least one acyl group, and the residual R^1, R^2 and R^3, when exist, are hydrogen atoms, or a mixture of two or more of the derivatives. As a further preferred one, there can be mentioned a CyD derivative wherein 50 % or more, particularly about 100% of R^1 and R^3 of the number of total 2×n are lower alkyl groups, and 50 % or more, particularly about 100% of R^2 of the number of n are C_{2-20} alkanoyl groups, or a mixture of two or more of the derivatives.

When harmony between the inclusion ability of the medicament and economical efficiency is taken into account, preferred is one which corresponds to n = 7 in the formula (I), i.e. β-CyD, and does not have a glucosyl group or maltosyl group as a branched sugar residue. Thus, as a still further preferred acylated alkylated derivative, there cas be mentioned a β-CyD derivative wherein 7 or more of 14 R^1s and R^3s are lower alkyl groups and 4 or more of 7 R^2s are C_{2-20} alkanoyl groups, or a mixture of two or more of the derivatives. As the mixture, there can, for example, be mentioned a mixture of two or more of compounds selected from the group consisting of compounds wherein 7 to 14 of all the R^1s and R^3s are alkyl groups. In this occasion, the number of R^2 which is a C_{2-20} alkanoyl group is the same or different between the two or more of compounds.

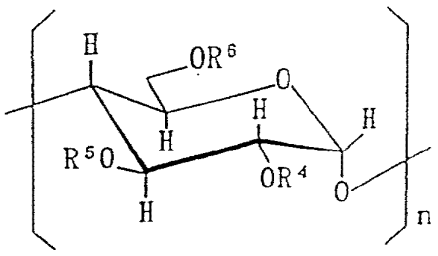
However, most preferably, there can be mentioned a β-CyD derivative wherein all of R^1s and R^3s are lower alkyl groups and all of R^2s are C_{2-20} alkanoyl groups, and a mixture wherein such derivatives are mainly (i.e, exceeding 50 %) contained.

The lower alkyl groups include straight-chain or branched alkyl groups having 1 to 6 carbon atoms, but as preferred ones, there can be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl groups, etc., and further preferred among them is a methyl group.

As to the C_{2-20} alkanoyl groups, the alkyl part may be straight-chain or branched, and as preferred ones, there can be mentioned acetyl, n-propanoyl, n-butanoyl, n-pentanoyl (or valeryl), n-hexanoyl (or caproyl), n-heptanoyl (or enanthoyl), n-octanoyl (or capryloyl), n-dodecanoyl (or lauroyl), n-tetradecanoyl (or myristoyl) and n-octadecanoyl (or stearoyl) groups, etc., and, above all, acetyl, n-propanoyl, n-butanoyl and n-hexanoyl are preferred, and further preferred among them is an acetyl group.

Thus, as particularly preferred ones among acylated alkylated CyD derivatives or mixtures of two or more of the derivatives according to the invention, there can be mentioned heptakis (2,6-di-O-methyl-3-acetyl)-β-CyD with a degree of substitution (D.S.) of 7 at the 3-position (hereinafter referred to as DMA-β-CyD, and the following abbreviations follow this) and mixtures mainly containing this DMA-β-CyD, or a mixture of acetylated DA-β-CyDs with a lower substitution (D.S. 3.5-6) at the 3-position.

Such an acylated alkylated CyD of the invention can be prepared by the following process, as another embodiment of the invention, which comprises reacting a partially alkylated CyD derivative represented by the formula (II)



(II)

wherein n is any of integers 6, 7 and 8, and the 1-position and the 4-position of the sugar residues at the both ends are mutually bound by a covalent bond,

R^4, R^5 and R^6 independently represent hydrogen atoms, lower alkyl groups, glucosyl groups or maltosyl groups, provided that R^4, R^5 and R^6 of the number of total $3 \times n$ composed of each n are, simultaneously, at least one lower alkyl group and at least one hydrogen atom, and the number of the glucosyl groups and maltosyl groups is at most 2,

or a mixture of the derivatives with an activated C_{2-20} alkanoic acid in a polar solvent, if necessary in the presence of a condensing agent.

The partially alkylated CyD derivatives of the formula (II) themselves are known or available on the market, but ones prepared according to preparation processes known per se can also be used. Further, as the activated C_{2-20} alkanoic acid, acid anhydrides or acid halides (chlorides, bromides) of alkanoic acids can be used, but preferably acid anhydrides can be mentioned. When an acid halide is used, it is desirable to make a basic organic amine such as triethylamine coexist as a hydrogen halide-capturing agent, but it is advantageous to use pyridine as a solvent and a hydrogen halide-capturing agent or condensing agent.

When an acid anhydride is used as an acylating reactant and pyridine is used as a solvent, the acyl

groups of the desired number can be introduced into a compound of the formula (II) by using pyridine in an amount enough to dissolve the CyD reactant and the acid anhydride reactant and carrying out reaction, usually, at a temperature around 80℃ for several hours to 72 hours. The desired acylated alkylated CyD derivatives can be isolated and purified from the thus obtained reaction mixture using solvent extraction, various chromatographies, and recrystallization per se known, but as stated above, they can also be separated, in a state of a mixture of two or more of the derivatives, from the reaction solvent and the unreacted reactant or the side reaction products. Usually, after the completion of the reaction, the reaction mixture is added dropwise into ice water to decompose the excess acid anhydride, and the desired CyD derivative is extracted with chloroform. Sodium carbonate is added to the extract, and the mixture is desalted and subjected to separation and purification using silica gel columns, and if necessary, subjected to recrystallization from an appropriate solvent. The desired CyD derivative can be obtained by concentrating the obtained substance to dryness. The structure of the obtained substance can be confirmed by mass spectrum, elementary analysis, etc.

As stated above, the thus obtained acylated alkylated CyD derivatives or mixtures of the derivatives of the invention have hemolytic activities and muscular irritation significantly lowered, compared with the previous CyDs, and have an action to solubilize water-sparingly soluble or insoluble medicaments at room temperature, and are useful as carriers or delivery tools for such medicaments.

Therefore, as another embodiment of the invention, there is provided a pharmaceutical preparation which comprises such an acylated alkylated CyD derivative or a mixture of two or more of the derivatives and

such a medicament in such a state that they are closely compounded. The "state that they are closely compounded" means such a state that the CyD derivative and the medicament are homogeneously mixed or such a state that the medicament and the CyD derivative form an inclusion compound.

The preparation in such a state can be prepared by sufficiently kneading the CyD derivative and the medicament, in an aqueous solvent (including a mixed solvent between methanol, ethanol, acetonitrile, dimethylformamide or the like and water), in such a state that the CyD derivative and the medicament are suspended or dissolved, using a kneader or the like regularly used for the preparation of formulations.

The pharmaceutical preparation can be administered in an administration form such as parenteral administration, namely intravenous injection, intramuscular injection, subcutaneous injection or topical administration to the skin or mucosa., but administration methods are not limited thereto, and it can also be administered by oral administration.

Medicaments or active ingredients applicable to the preparation according to the invention may be any medicaments including water-soluble or sparingly soluble ones, so long as they meet the objects of the invention, but there can, generally, be mentioned water-sparingly soluble or insoluble medicaments, or unstable medicaments.

Further suitable active ingredients are those which exert a local physiological effect, as well as those which exert a systemic effect, either after penetrating the mucosa or in the case of oral administration - after transport to the gastro-intestinal tract with saliva. The dosage forms prepared from the compositions according to the present invention are particularly suitable for active ingredients which exert their activ-

ity during an extended period of time, i.e. drugs having a half-life of at least several hours. Examples thereof are: analgesic and anti-inflammatory drugs (NSAIDs, flurbiprofen, fentanyl, indomethacin, ketoprofen, nabumetone, paracetamol, piroxicam, tramadol); anti-arrhythmic drugs (procainamide, quinidine, verapamil); antibacterial and antiprotozoal agents (amoxicillin, ampicillin, benzathine penicillin, benzylpenicillin, cefaclor, cefadroxil, cefprozil, cefuroxime axetil, cephalexin, chloramphenicol, chloroquine, ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxycycline, erythromycin, flucloxacillin, halofantrine, isoniazid, kanamycin, lincomycin, mefloquine, minocycline, nafcillin, neomycin, norfloxacin, ofloxacin, oxacillin, phenoxymethyl-penicillin, pyrimethamine-sulfadoxime, streptomycin); anti-coagulants (warfarin); antidepressants (amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dothiepin, doxepin, fluoxetine, gepirone, imipramine, lithium carbonate, mianserin, milnacipran, nortriptyline, paroxetine, sertraline; 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridin-2(1H)-yl]-ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one); anti-diabetic drugs (glibenclamide, metformin); anti-epileptic drugs (carbamazepine, clonazepam, ethosuximide, phenobarbitone, phenytoin, primidone, topiramate, valpromide); antifungal agents (amphotericin, clotrimazole, econazole, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole nitrate, nystatin, terbinafine, voriconazole); antihistamines (astemizole, cinnarizine, cyproheptadine, decarboethoxyloratadine, fexofenadine, lunarizine, levocabastine, loratadine, norastemizole, oxatomide, promethazine, terfenadine); anti-hypertensive drugs (captopril, enalapril, ketanserin, lisinopril, minoxidil, prazosin, ramipril, reserpine, terazosin); anti-muscarinic agents (atropine sulphate, hyoscine);

antivirals (acyclovir, AZT, ddC, ddI, ganciclovir, loviride, tivirapine, 3TC, delavirdine, indinavir, nelfinavir, ritonavir, saquinavir); antineoplastic agents and antimetabolites (adriamycine, cladribine, cisplatin, dactinomycin, daunorubicin, doxorubicin, etoposide, irinotecan, mitomycin, mitoxantrone, tamoxifen, taxol, taxotere, topotecan, trimetrexate, vincristine, vinblastine); anti-migraine drugs (almotriptan, alniditan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan); anti-Parkinsonian drugs (bromocryptine mesylate, levodopa, selegiline); antipsychotic, hypnotic and sedating agents (alprazolam, buspirone, chlordiazepoxide, chlorpromazine, clozapine, diazepam, fluphenthixol, fluphenazine, flurazepam, 9-hydroxyrisperidone, lorazepam, mazapertine, olanzapine, oxazepam, pimozide, pipamperone, piracetam, promazine, risperidone, selfotel, seroquel, sertindole, sulpiride, temazepam, thiothixene, triazolam, trifluperidol, ziprasidone, zolpidem); anti-stroke agents (lubeluzole, lubeluzole oxide, riluzole, aptiganel, eliprodil, remacemide); antitussive (dextromethorphan, laevodropropizine); beta-adrenoceptor blocking agents (atenolol, carvedilol, metoprolol, nebivolol, propanolol); cardiac inotropic agents (amrinone, digitoxin, digoxin, milrinone); corticosteroids (beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone); disinfectants (chlorhexidine); diuretics (acetazolamide, frusemide, hydrochlorothiazide, isosorbide); enzymes; essential oils (anethole, anise oil, caraway, cardamom, cassia oil, cineole, cinnamon oil, clove oil, coriander oil, dementholised mint oil, dill oil, eucalyptus oil, eugenol, ginger, lemon oil, mustard oil, neroli oil, nutmeg oil, orange oil, peppermint, sage, spearmint, terpineol, thyme); gastro-intestinal agents

(cimetidine, cisapride, clebopride, diphenoxylate, domperidone, famotidine, lansoprazole, loperamide, loperamide oxide, mesalazine, metoclopramide, mosapride, nizatidine, norcisapride, olsalazine, omeprazole, pantoprazole, perprazole, prucalopride, ranitidine, rabeprazole, ridogrel, sulphasalazine); haemostatics (aminocaproic acid); lipid regulating agents (atorvastatin, lovastatin, pravastatin, probucol, simvastatin); local anaesthetics (benzocaine, lignocaine); opioid analgesics (buprenorphine, codeine, dextromoramide, dihydrocodeine, hydrocodone, oxycodone, morphine); parasympathomimetics (eptastigmine, galanthamine, metrifonate, neostigmine, physostigmine, tacrine, donepezil, rivastigmine, milameline, sabcomeline, talsaclidine, xanomeline, memantine, lazabemide); sex hormones (oestrogens: conjugated oestrogens, ethinyloestradiol, mestranol, oestradiol, oestriol, oestrone; progestogens; chlormadinone acetate, cyproterone acetate, 17-deacetyl norgestimate, desogestrel, dienogest, dydrogesterone, ethynodiol diacetate, gestodene, 3-keto desogestrel, levonorgestrel, lynestrenol, medroxy-progesterone acetate, megestrol, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, progesterone, quingestanol acetate); stimulating agents (sildenafil); vasodilators (amlodipine, buflomedil, amyl nitrite, diltiazem, dipyridamole, glyceryl trinitrate, isosorbide dinitrate, lidoflazine, molsidomine, nicardipine, nifedipine, oxpentifylline, pentaerythritol tetranitrate).

In the preparation according to the invention, the compounding ratio between the acylated alkylated CyD and the medicament can be an any ratio so long as it meets the objects, but in view of controlling the release of the medicament from the preparation, the ratio of the acylated alkylated CyD : the medicament can be made to be 1 : 4 to 4 : 1, preferably 1 : 2 to 2 : 1, in

terms of mole ratio.

In the preparation of the invention, pharmaceutically acceptable other auxiliaries or additives can, if necessary, be incorporated in a range not to have bad influence on the objects of the invention. As such auxiliaries or additives, there can be mentioned stabilizers, dissolution aids, suspending agents, emulsifying agents, buffering agents, preservatives, isotonizing agents, or other proper additives, which are used regularly in the technical field.

The invention is specifically described below by examples, but the invention is not limited by these examples.

Example 1 Synthesis of DMA-β-CyD

DM-β-CyD (12 g) was dissolved in 60 mL of anhydrous pyridine, and 25 mg of 4-dimethylaminopyridine was added. Then, 12 mL of acetic anhydride was gradually added dropwise, and the mixture was subjected to reaction at 80℃ for 24 hours. After the completion of the reaction, the mixture was added dropwise into ice water to decompose the excess acid anhydride, and extracted with chloroform. Sodium carbonate was added to the organic phase to desalt it, and the mixture was subjected to separation and purification using a silica gel column. The obtained substance was concentrated to dryness to give the desired DMA-β-CyD (D.S. 7). This CyD derivative had a melting point of 113 to 117℃, and its solubility in water at 25℃ exceeded 50 mg/dl. The resulting DMA-β-CyD (D.S. 7) was recrystallized from water to give white crystals (yield 60%) having a melting point of 126℃. Its mass spectrum and ^{1}H-NMR spectrum are shown in Fig. 1 and Fig. 2, respectively.

FAB MS (negative mode) *m/z* 1777 [M+*m*-nitrobenzyl alcohol (matrix)-H); ^{1}H-NMR ($CDCl_3$) d 5.16 (t, 1H, CyD H-3), 5.00 (d, 1H, CyD H-1), 3.91-3.87 (m, 2H, CyD H-5 and H-6b), 3.79 (t, 1H, CyD H-4), 3.54 (d, 1H,

CyD H-6a), 3.37 (s, 3H, 6-CH_3), 3.33 (s, 3H, 2-CH_3), 3.21 (dd, 1H, CyD H-2), 2.04 (s, 3H, 3-CH_3).

Example 2 Synthesis of acetylated DM-β-CyD with a lower substitution at the 3-position

The acetylated DM-β-CyD was prepared by using a small amount of the acid anhydride (4.6 g, 45 mmol) to DM-β-CyD (10 g, 7.5 mmol). The other condition of preparation was identical to that described in Example 1, except for the recrystallization due to the face that it was a mixture of components with different D.S.s. The D.S. value was determined by a peak ratio of the CyD anomeric proton (H-1) and the methyl proton of acetyl groups in ^{1}H-NMR spectra (see Fig. 3), and was 3.8. The mixture is hereinafter referred to as DMA4-β-CyD.

Example 3 Synthesis of butyrated DM-β-CyD

DM-β-CyD (5 g) was dissolved in 25 mL of anhydrous pyridine, and 9 mL of n-butyric anhydride was added, and the mixture was subjected to reaction at 80℃ for 24 hours. After the completion of the reaction, the mixture was added dropwise into ice water to decompose the excess acid anhydride, and extracted with chloroform. Sodium carbonate was added to the extract to desalt it, and the mixture was subjected to separation and purification using a silica gel column. The obtained substance was concentrated to dryness to give the desired butyrated DM-β-CyD. This CyD derivative had a melting point of 108 to 111℃. Its ^{1}H-NMR spectrum is shown in Fig. 4.

Example 4 Synthesis of octanoylated DM-β-CyD

DM-β-CyD (5 g) was dissolved in 25 mL of anhydrous pyridine, and 16 mL of octanoic anhydride was added, and the mixture was subjected to reaction at 80℃ for 24 hours. After the completion of the reaction, the mixture was added dropwise into ice water to decompose the excess acid anhydride, and extracted with chloroform. Sodium carbonate was added to the extract to

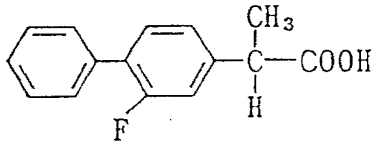
desalt it, and the mixture was subjected to separation and purification using a silica gel column. The obtained substance was concentrated to dryness to give the desired octanoylated DM-β-CyD. This CyD derivative was an oily substance at 25℃. Its ^{1}H-NMR spectrum is shown in Fig. 5.

Characteristic tests

(1) Determination of stability constant of DMA-β-CyD

In this test, the inclusion properties of DMA-β-CyD was compared with those of the parent β-CyD and DM- and TM-β-CyDs.

The stability constant between DMA-β-CyD and flurbiprofen was determined by the solubility method i.e., according to the method of Higuchi, T. et al., Adv. Anal. Chem. Instr. 1965, 4, 117-212. The stability constants between β-CyD, DM-β-CyD or TM-β-CyD and flurbiprofen determined simultaneously for comparison are also shown in Table 1.



Flurbiprofen

Table 1:

Compound	Stability constant (M^{-1})
β-CyD	3613
DM-β-CyD	8055
TM-β-CyD	1655
DMA-β-CyD	1212

These results suggest that DMA-β-CyD has the same inclusion ability as TM-β-CyD, although it is inferior in inclusion ability to DM-β-CyD.

(2) Test on hemolytic properties of DMA-β-CyD and DMA4-β-CyD

In this test on hemolytic properties, 6 to 7 mL of blood was taken from the auricular vein of a white rabbit, 1 mL of a preserved erythrocyte solution was added, and the mixture was gently mixed. To this was added 4 to 5 mL of 10 mM isotonized phosphate buffer (pH 7.4), the mixture was gently mixed and centrifuged at 1,000 g for 5 minutes, and the supernatant was removed. This washing operation was repeated three times, 10 mM isotonized phosphate buffer (pH 7.4) was added to 1 mL of the resultant solution to make the volume 20 mL, and thereby a 5 % erythrocyte suspension was prepared.

The CyD derivative of various concentrations was diluted with 10 mM isotonized phosphate buffer (pH 7.4), and the resultant each dilution was incubated at 37℃. Then 4 mL of this dilution was taken, 0.2 mL of the 5 % erythrocyte suspension was added, and the mixture was incubated at 37℃ for 30 minutes. The mixture was centrifuged at 1,000 g for 5 minutes, 3 mL of the supernatant was measured for absorbance at 543 nm, and thereby its hemolytic activity was determined. Further, the specimen was observed visually using a microscope. The obtained results are shown in Fig. 6. To the 5 % erythrocyte suspension was added 100 mM DMA-β-CyD (D.S. 7), DMA4-β-CyD (D.S. 3.8), β-CyD, DM-β-CyD, TM-β-CyD, 2-HP-β-CyD (D.S. 4.8) (see Shiotani, K. et al. Pharm. Res. 1995, 12, 78-84) or subfobutyl ether β-CyD (D.S. 3.5)

(see ibid), the above treatment was carried out, and then observation by a microscope was made.

It is apparent that the hemolytic activity of DMA-β-CyDs was weaker than those of β-CyD, DM-β-CyD and TM-β-CyD. For example, the hemolysis began at about 2 mM, 0.5 mM and 1 mM, and the concentrations to induce 50% hemolysis were about 4 mM, 1 mM and 2 mM for β-CyD, DM-β-CyD and TM-β-CyD, respectively. On the other hand, the hemolysis of DMA4-β-CyD with D.S. 3.8 began at about 12 mM, and its 50% hemolysis concentration was about 22 mM. In the case of DMA-β-CyD with D.S. 7, no hemolyis was observed up to 100 mM. The hemolytic activity of DMA-β-CyDs was weaker than those of 2-HP (D.S. 4.8) and sulfobutyl ether of β-CyD (D.S. 3.5).

(3) Determination of the released amount of cholesterol from the intact erythrocytes of rabbits treated with DMA-β-CyD or DMA4-β-CyD

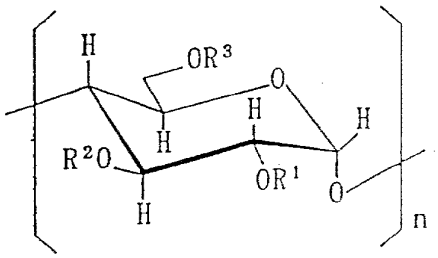
Each DMA-β-CyD, DMA4-β-CyD, DM-β-CyD was diluted with 10 mM isotonized phosphate buffer (pH 7.4), and the dilution was incubated at 37℃. Then, 4 mL of the dilution was taken, 0.2 mL of the 5 % erythrocyte suspension was added, and the mixture was incubated at 37℃ for 30 minutes. The mixture was centrifuged at 1,000 g for 5 minutes, 5 mL of chloroform was added to 3 mL of the supernatant, and the mixture was shaken for 30 minutes to make extraction. The chloroform layer was taken, and concentrated to give a specimen. The specimen was assayed for cholesterol amount using a Cholesterol E-Test Wako (made by Wako Pure Chemical Industries, Ltd.). The obtained results are shown in Fig. 7.

One of the causes of CyD-induced hemolysis is

known to be extractions of cholesterol and phospholipids from erythrocytes through the inclusion complex formation. Therefore, in this test, the cholesterol release behavior from rabbit erythrocytes by the addition of DMA-β-CyD or DMA4-β-CyD was investigated and compared with the cholesterol release behaviors of a control (an isotonic buffer without CyDs) and DM-β-CyD. Figure 7 shows the released amounts of cholesterol from the intact erythrocytes of rabbits treated with β-CyDs in 10 mM phosphate buffer (pH 7.4) at 37℃. DM-β-CyD induced about 80% release of cholesterol at a concentration of 0.5 mM at which the hemolyis only slightly occurred (see Figure 6). On the other hand, DMA-β-CyDs induced only 10% release of cholesterol at the same concentration, and this release was the same as that of the control experiment conducted in the isotonic buffer.

CLAIMS

1. An acylated alkylated cyclodextrin derivative represented by the formula (I)



(I)

wherein n is any of integers 6, 7 and 8, and the 1-position and the 4-position of the sugar residues at the both ends are mutually bound by a covalent bond,

R^1, R^2 and R^3 independently represent hydrogen atoms, lower alkyl groups or C_{2-20} alkanoyl groups, or in some case, represent glucosyl groups or maltosyl groups whose hydroxyl group(s) may be replaced with lower alkyloxy group(s) or C_{2-20} alkanyloxy group(s),

provided that any of R^1, R^2 and R^3 of the number of total $3 \times n$ composed of each n are simultaneously at least one lower alkyl group and at least one C_{2-20} alkanoyl group, and the residual groups, when exist, are hydrogen atoms or the glucosyl groups or maltosyl groups of the number of up to at most 2,

or a mixture of two or more of the derivatives.

2. The acylated alkylated cyclodextrin derivative

or mixture of two or more of the derivatives according to claim 1 wherein 50 % or more of R^1 and R^3 of the number of total $2 \times n$ are lower alkyl groups, the residual R^1 and R^3 and R^2 are at least one C_{2-20} alkanoyl group, and the residual R^1, R^2 and R^3, when exist, are hydrogen atoms.

3. The acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to claim 1 wherein R^1 and R^3 are lower alkyl groups, 50 % or more of R^2 are C_{2-20} alkanoyl groups, and the residual R^2, when exist, are hydrogen atoms.

4. The acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to claim 1 wherein R^1 and R^3 are lower alkyl groups, and 50 % or more of R^2 of the number of n are acyl groups.

5. The acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to any of claims 1 to 4 wherein the lower alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl or sec-butyl, and the alkanoyl groups are acetyl, n-propanoyl, n-butanoyl, n-pentanoyl, n-hexanoyl, n-heptanoyl, n-octanoyl, n-dodecanoyl, n-tetradecanoyl or n-octadecanoyl.

6. The acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to any of claims 1 to 5 wherein the lower alkyl groups are methyl groups, and the alkanoyl groups are acetyl groups.

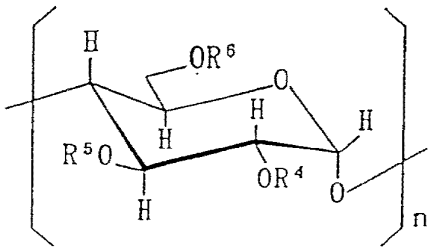
7. The acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to any of claims 1 to 6 wherein n is 7 in the formula

(I).

8. Heptakis (2,6-di-O-methyl-3-O-acetyl)-β-cyclodextrine; heptakis (2,6-di-O-methyl-3-O-butyryl)-β-cyclodextrine; or heptakis (2,6-di-O-methyl-3-O-octanoyl)-β-cyclodextrine.

9. A mixture of acetylated heptakis (2,6-di-O-methyl)-β-cyclodextrines having an average degree of acetyl-substitution of about 3.8 at the 3-position.

10. A process for preparing an acylated alkylated cyclodextrin derivative represented by the formula (I) according to claim 1 or a mixture of two or more of the derivatives which comprises reacting a partially alkylated cyclodextrin derivative represented by the formula (II)



(II)

wherein n is any of integers 6, 7 and 8, and the 1-position and the 4-position of the sugar residues at the both ends are mutually bound by a covalent bond,

R^4, R^5 and R^6 independently represent hydrogen atoms, lower alkyl groups, glucosyl groups or maltosyl groups, provided that R^4, R^5 and R^6 of the number of total $3 \times n$ composed of each n are, simultaneously, at least one lower alkyl group and at least one hydrogen atom, and the number of the glucosyl groups

and maltosyl groups is at most 2,

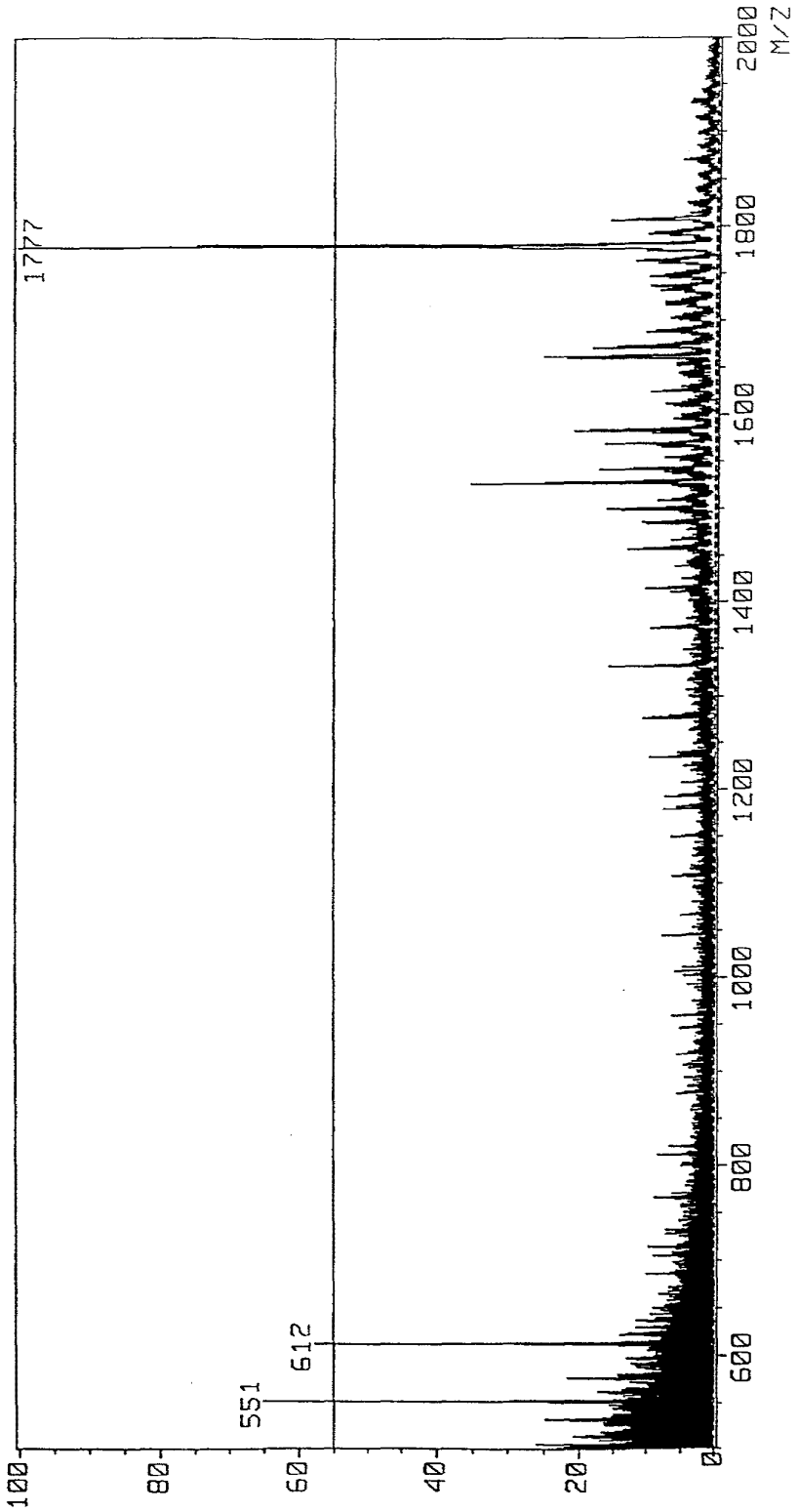
or a mixture of the derivatives with an activated C_{2-20} alkanoic acid in a polar solvent, if necessary in the presence of a condensing agent to acylate the compound(s) of the formula (II).

11. A pharmaceutical preparation which comprises the acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to any of claims 1 to 9 and a medicament in such a state that they are closely compounded.

12. The pharmaceutical preparation according to claim 11 wherein the medicament is selected from the group consisting of nonsteroidal antirheumatic agents, steroids, cardiac glycosides, benzodiazepine derivatives, benzimidazole derivatives, piperidine derivatives, piperazine derivatives, imidazole derivatives and triazole derivatives.

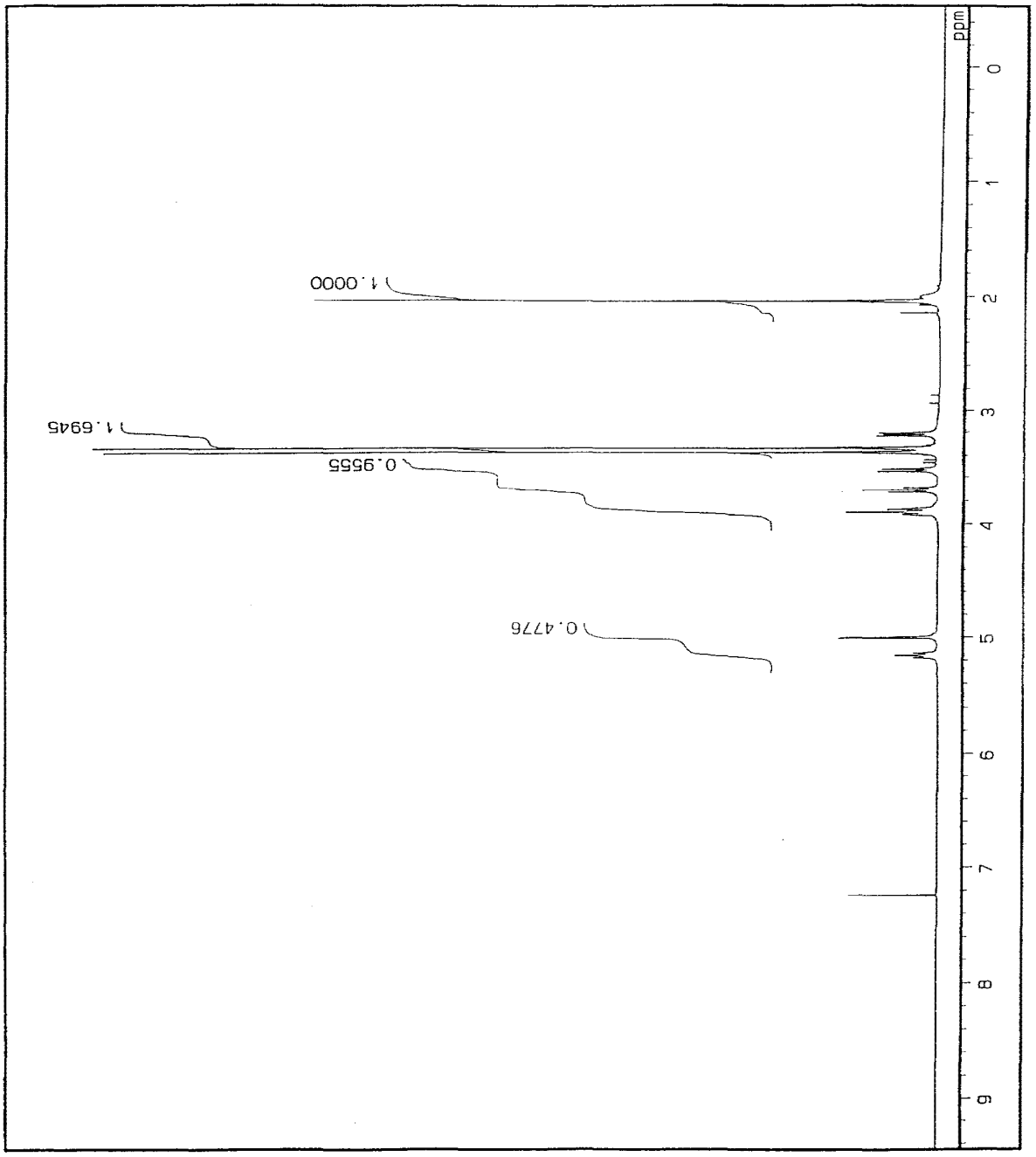
13. A process for preparing a pharmaceutical preparation according to claim 11 or 12 which comprises kneading closely the acylated alkylated cyclodextrin derivative or mixture of two or more of the derivatives according to any of claims 1 to 6 and a medicament in an aqueous solvent, and then, if necessary, removing the solvent.

FIG. 1


1777
612
551
100
80
60
40
20
0
600
800
1000
1200
1400
1600
1800
2000
M/Z

123

FIG. 2



124

FIG. 3

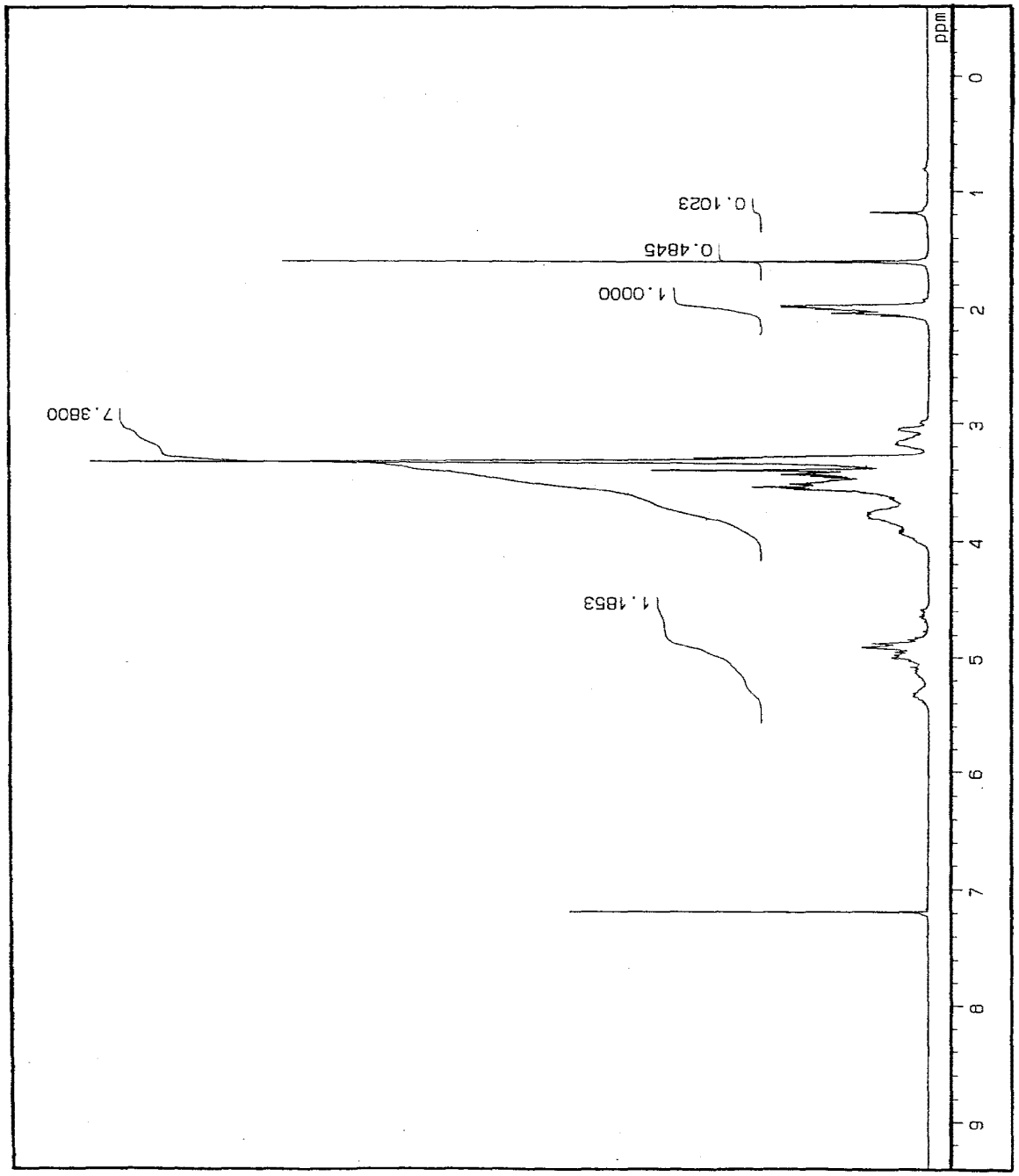
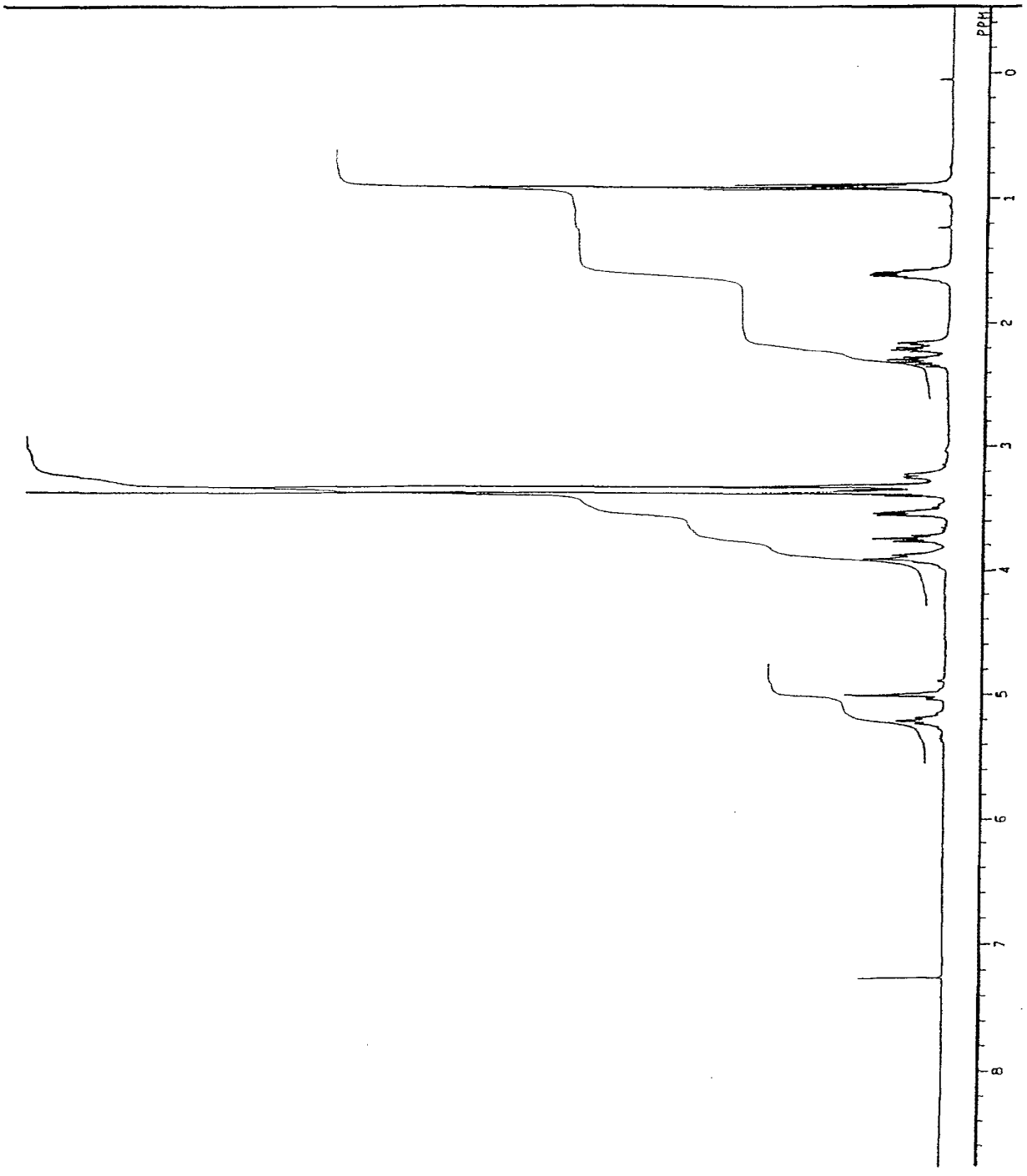
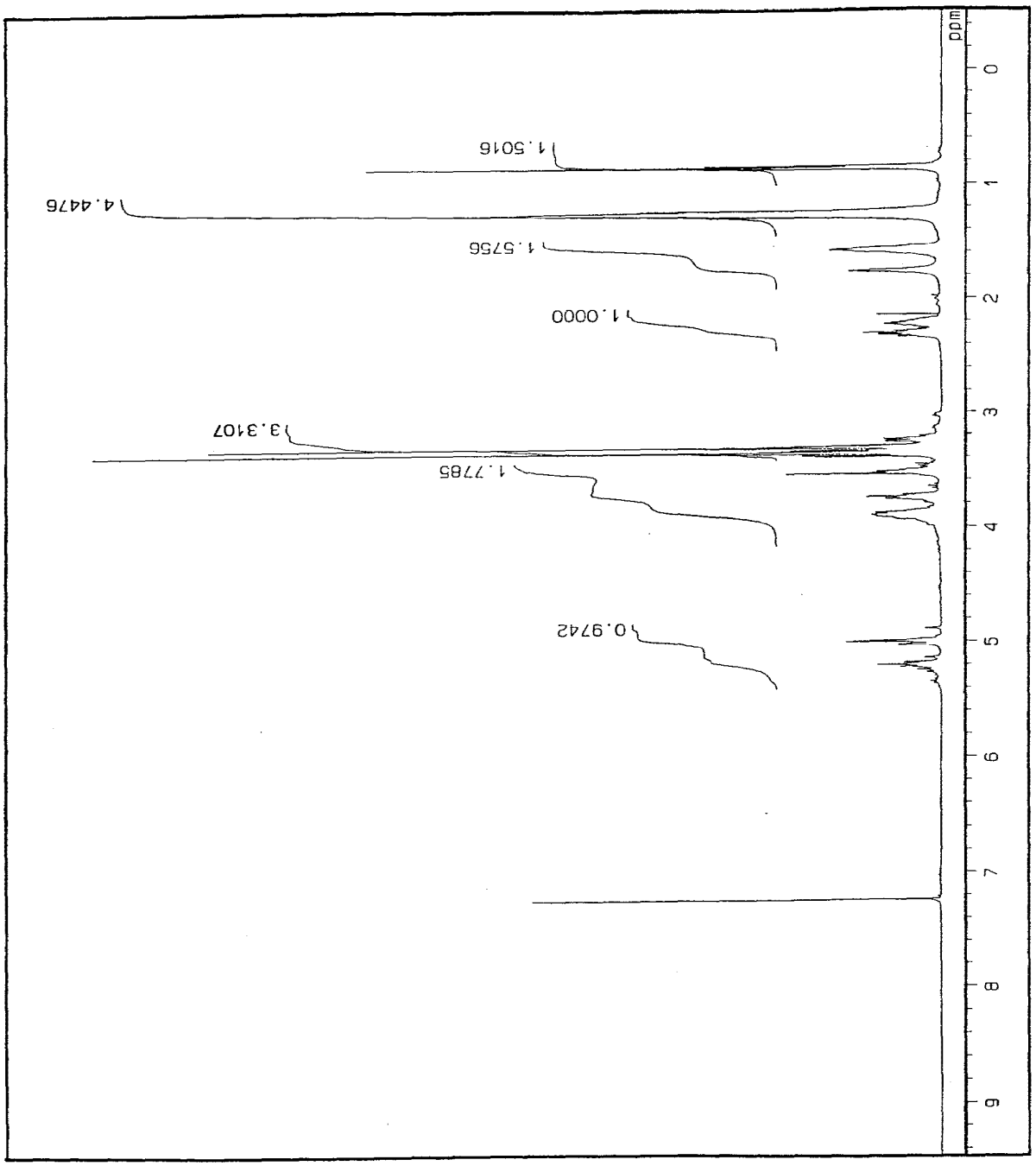


FIG. 4



126

FIG. 5



127

FIG. 6

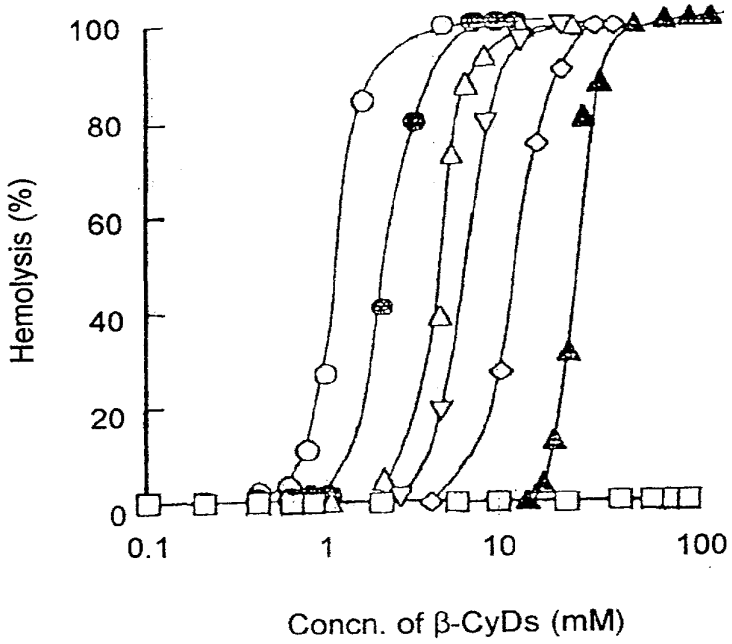
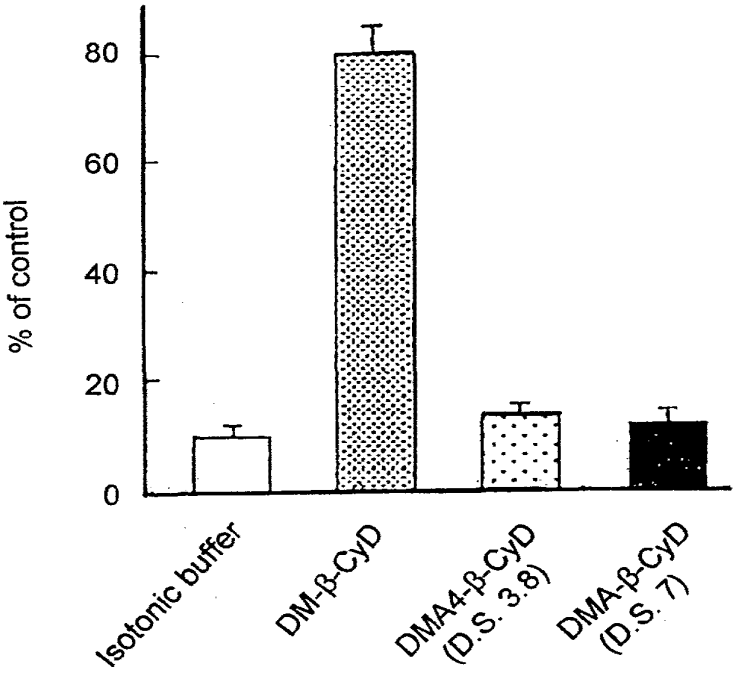

100
80
60
40
20
0
Hemolysis (%)
0.1
1
10
100
Concn. of β-CyDs (mM)

FIG. 7


80
60
40
20
0
% of control
Isotonic buffer
DM-β-CyD
DMA4-β-CyD (D.S. 3.8)
DMA-β-CyD (D.S. 7)

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/JP 99/02806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08B37/16 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89 09235 A (MACHEREY-NAGEL GMBH) 5 October 1989 (1989-10-05) claims 1-7; example 3	1-4,10
X	EP 0 312 352 A (CHINOIN) 19 April 1989 (1989-04-19) page 3, line 17,18 page 13, line 60 - line 64 page 14, line 34 - line 40	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 August 1999	18/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lensen, H

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ational Application No
PCT/JP 99/02806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8909235 A	05-10-1989	DE 3810737 A	12-10-1989
		EP 0407412 A	16-01-1991
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		US RE36092 E	09-02-1999
		US 5198429 A	30-03-1993
EP 312352 A	19-04-1989	JP 1198603 A	10-08-1989
		US 5008386 A	16-04-1991

Espacenet

Bibliographic data: WO9855148 (A1) — 1998-12-10

PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLODEXTRINS

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Applicant(s):	JANSSEN PHARMACEUTICA NV [BE]; VANDECRUYS ROGER PETRUS GEREBE [BE] ±

Classification:	**- international:**	***A61K47/12; A61K47/30; A61K47/40; A61K8/73; A61K9/14; A61K9/48; A61Q3/00; A61K47/38;*** (IPC1-7): A61K47/48; A61K9/14; A61K9/48
	- European:	A61K8/73; A61K8/73C; A61K8/73T; A61K9/00M3; A61K9/14H4; A61K9/14H6; A61K9/48H4; A61K9/48H6; A61Q3/00
Application number:	WO1998EP03189 19980527	
Priority number(s):	GB19970011643 19970605	
Also published as:	ZA9804849 (A) US2002150616 (A1) PT998304 (E) NO995925 (A) KR20010005852 (A) JP2002511073 (A) HU0004924 (A2) ES2206949 (T3) EP0998304 (A1) EP0998304 (B1) DK998304 (T3) DE69817363 (T2) CN1258220 (A) CA2292506 (A1) AU8108198 (A) AT247489 (T) AR012927 (A1) less	

Abstract of WO9855148 (A1)

The invention provides a novel pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLODEXTRINS

(57) Abstract

The invention provides a novel pharmaceutical composition comprising a no more than sparingly water–soluble drug compound, a cyclodextrin, a physiologically tolerable water–soluble acid, and a physiologically tolerable water–soluble organic polymer.

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PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLODEXTRINS

This invention relates to novel pharmaceutical compositions, in particular compositions and dosage forms providing improved drug release and uptake on administration into externally voiding body cavities (e.g. the gi tract) or on topical administration, especially for acid solubilized drug compounds.

Many drug compounds, while possessing desired therapeutic properties, are used inefficiently due to their poor water solubilities. Thus for example where such compounds are administered orally, only a small fraction of the drug is taken up into the blood during transit of the gi tract. As a result, to achieve adequate drug uptake it may be necessary to administer high doses of the drug compound, to prolong the period of drug administration or to make frequent administrations of the drug compound. Indeed, the poor solubility and hence poor bioavailability of a drug may cause an alternative drug, perhaps one with undesired side effects or one which requires invasive administration (e.g. by injection or infusion), to be used in place of the poorly soluble drug.

One approach to poor solubility is to derivatise the drug molecule to introduce water solubilizing groups, e.g. ionic groups such as carboxyl groups or non-ionic groups such as polyhydroxyalkyl groups, so as to produce a more soluble derivative. This approach however is not always successful as it may not be possible to maintain adequately high therapeutic efficacy and adequately low toxicity or other side effects. Thus one example of a poorly water soluble drug which has not been superseded by a solubilized derivative is the antifungal agent itraconazole.

Attempts have therefore been made to enhance the uptake of drugs such as itraconazole by increasing the surface area of the drug compound exposed to saliva or gastric fluid, and hence promote dissolution of the drug compound, by thinly coating the drug compound onto essentially inert carrier particles, e.g. sugar beads. This however has the drawback that the volume of solid composition required to administer a given quantity of the drug compound is quite high since the carrier contributes significantly to the overall administration volume. Since administration of large volume capsules or tablets, or of large quantities of smaller volume capsules or tablets, provides difficulties for the patient, the drawbacks of this approach are obvious.

Yet another approach has been to administer the drug compound in the form of a solution of the drug compound and a drug complexing agent such as a cyclodextrin. This approach has limitations also in that the dosage volume is constrained by the

solubilizing power of the complexing agent, readily unitized solid dosage forms can not be used, and there is no gradual release of the drug compound for biological uptake.

However, we have now found that by combining such drug compounds with a cyclodextrin, a water-soluble acid and a water-soluble organic polymer, an administration form may be produced which surprisingly improves the biological uptake of the drug compound, in particular a form which can surprisingly improve the time profile for the drug content of the plasma of the patient (*i.e.* the pharmacokinetic profile defined by such parameters as AUC, t_{max}, C_{max}, etc.).

Thus viewed from one aspect the invention provides a pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

Viewed from a further aspect the invention provides the use of a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer for the manufacture of a pharmaceutical composition according to the invention for use in a method of therapy or diagnosis of the human or non-human animal (e.g. mammalian, reptilian or avian) body.

Viewed from a still further aspect the invention provides a method of therapy or diagnosis of the human or non-human animal (e.g. mammalian, reptilian or avian) body which comprises administering to said body a therapeutically or diagnostically effective dose of a pharmaceutical composition, the improvement comprising using as said composition a composition according to the present invention.

The compositions of the invention may if desired be aqueous, but in general will preferably be substantially water-free, e.g. containing up to 3% by weight, preferably less than 1% by weight water, and most preferably less than 0.5% water, but may be mixed with water immediately before administration or may be coated and dispersed in an aqueous medium whereby the coating is only broken down after administration. Such aqueous compositions are deemed to fall within the scope of the invention. Depending on the selection of components, the compositions of the invention may be liquid, solid or semi-solid - e.g. gel-like. Preferably the compositions are non-freeflowing at ambient temperature (e.g. 21°C), other than as free flowing particulates. Thus the compositions at ambient temperature are preferably solids or semi-solids or, less preferably, highly viscous fluids.

In the compositions of the invention the drug compound, acid, cyclodextrin and organic polymer are intimately admixed.

Thus where the composition is particulate, the acid, drug compound, cyclodextrin and organic polymer are mixed together within the particles (e.g. at the molecular level following solvent removal from a solution of these components). Granulate mixtures where individual particles do not contain all four components, or have cores of one or more components coated with other components are not preferred. This intimate admixture is important since the effects of the components are complimentary at the microscopic level during dissolution of the compositions of the invention.

Preferably, all components are dispersed so as to form a system that is chemically and physically uniform or homogenous throughout, or consists of one phase as defined in thermodynamics ; such a dispersion will be called a glass thermoplastic phase or system hereinafter. The components of the glass thermoplastic system are readily bioavalaible to the organisms to which they are administered. This advantage can probably be explained by the ease with which said glass thermoplastic system can form liquid solutions when contacted with a body liquid such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a glass thermoplastic system is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

As the cyclodextrin in the compositions of the invention, there may be used any of the physiologically tolerable water-soluble substituted or unsubstituted cyclodextrins or physiologically tolerable derivatives thereof, e.g. α-, β- or γ-cyclodextrins or derivatives thereof, in particular derivatives wherein one or more of the hydroxy groups are substituted, e.g. by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy)alkyl groups, wherein each alkyl or alkylene moiety preferably contains up to six carbons.

Substituted cyclodextrins which can be used in the invention include polyethers, e.g. as described in US Patent 3,459,731. In general, to produce these, unsubstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst. Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can react with yet another molecule of alkylene oxide, the average molar substitution

(MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit. In the cyclodextrin derivatives for use in the compositions according to the present invention the M.S. is conveniently in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly it is about 0.4. M.S. values determined by NMR or IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}-alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl-C_{1-6}alkyl groups or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxy-C_{2-4}alkyl or carboxy-C_{1-2}alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl.

In the foregoing definitions, the term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as methyl, ethyl 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

Such ethers can be prepared by reacting a cyclodextrin with an appropriate O-alkylating agent or a mixture of such agents in a concentration selected such that the desired cyclodextrin ether is obtained. The reaction is preferably conducted in a solvent in the presence of a base. With such ethers, the degree of substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more particularly 0.3 to 1, and the MS is in the range of 0.125 to 10, in particular 0.3 to 3 and more particularly 0.3 to 1.5.

Of particular utility in the present invention are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin. Such alkyl ethers may for example be methyl ethers with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin and

propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

Especially suitable cyclodextrins are β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

Besides simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used.

Other cyclodextrins are described for example in Chemical and Pharmaceutical Bulletin 28: 1552-1558 (1980), Yakugyo Jiho No. 6452 (28 March 1983), Angew. Chem. Int. Ed. Engl. 19: 344-362 (1980), US-3,459,731, EP-A-0,149,197, EP-A-0,197,571, US-4,535,152, WO-90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: "Cyclodextrin Technology" by József Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12, Ed. by M.L. Wolfrom, Academic Press, New York in the chapter The Schardinger Dextrins by Dexter French at p. 189-260; "Cyclodextrins and their Inclusion Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A.P. Croft and R.A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); Irie et al. Pharmaceutical Research, 5, p. 713-716, (1988); Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118,218; DE-3,317,064; EP-A-94,157; US-4,659,696; and US-4,383,992.

More recent examples of substituted cyclodextrins include sulfobutylcyclodextrins (US-5,134,127-A). Their use is also envisaged in the present invention.

The cyclodextrin used is preferably a β-cyclodextrin, in particular hydroxypropyl-β-cyclodextrin. The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of from 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

Nevertheless, the choice of cyclodextrin may be directed by the ability of the selected drug compound to be complexed by a particular cyclodextrin - thus the cyclodextrins

with greater affinity for the particular drug compound may be preferred.

In the compositions of the invention, the cyclodextrin is preferably present at 5 to 70% by weight, more preferably 8 to 55%, most preferably 10 to 45% by weight (relative to the total weight of cyclodextrin, acid, organic polymer and drug). The quantity of cyclodextrin used however will generally be dependent on the quantity of drug and the molar ratio of cyclodextrin to drug will preferably lie in the range 100:1 to 1:5, especially 50:1 to 1:2, more especially 10:1 to 1:1.

The acid used in the compositions of the invention may be any of the water-soluble physiologically tolerable acids, in particular any of the inorganic or, more preferably, organic acids conventionally used in the preparation of acid salts of drug compounds, e.g. citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic and ascorbic acids.

Tartaric acid and more especially citric acid are preferred since the salts they form with drug compounds usually have a reduced tendency to precipitate from aqueous solutions. In general however, any acid which is not so strong as to cause degradation of the cyclodextrin and yet which is capable, on the addition of water, of generating a low pH environment, preferably lower than pH 4 and ideally about pH 2, may be used. The acid may be in liquid (e.g. solution) or solid form; however acids which are solid at ambient conditions in their anhydrous or hydrate forms will generally be preferred.

In the compositions of the invention, the acid will preferably be present at 1 to 95% by weight, preferably 5 to 90% by weight, more preferably 20 to 80%, and especially preferably 35 to 60% by weight (relative to the total weight of cyclodextrin, drug compound, organic polymer and acid). The amount of acid used will be dependent upon the selected acid and drug compound, but in general an increase in the relative proportion of acid will result in an acceleration of drug dissolution on contact with water. The amount of acid used will normally be at least the amount necessary to form a 1:1 salt with the drug compound.

In general, the acid will form a significant proportion of dosage forms that dissolve rapidly in body fluids. Typically, they will comprise from 50 to 95% by weight of acid, preferably 50 to 90% by weight, more preferably 55 to 60% by weight. Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising an organic drug compound, a water-soluble physiologically tolerable acid, a water-soluble physiologically tolerable cyclodextrin and a water-soluble physiologically

tolerable organic polymer, characterised in that the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1, preferably no more than 1.5:1, especially preferably no more than 1:1, and particularly preferably no more than 0.9:1, especially no more than 0.5:1.

The organic polymer used in the compositions of the invention may be any of the physiologically tolerable water soluble synthetic, semi-synthetic or non-synthetic organic polymers.

Thus for example the polymer may be a natural polymer such as a polysaccharide or polypeptide or a derivative thereof, or a synthetic polymer such as a polyalkylene oxide (e.g. PEG), polyacrylate, polyvinylpyrrolidone, etc. Mixed polymers, e.g. block copolymers and glycopeptides may of course be used.

It is believed that the effect of the organic polymer arises from an enhancement in viscosity which serves to stabilize supersaturated solutions of the drug compound on dissolution of the composition of the invention. Thus the polymer conveniently has a molecular weight in the range 500D to 2 MD, and conveniently has an apparent viscosity of 1 to 100 mPa.s when in a 2% aqueous solution at 20°C. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectins such as sodium carboxymethylamylopectin,
- chitin derivates such as chitosan,
- heparin and heparinoids,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum and xanthan gum,
- polyacrylic acids and the salts thereof,

- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing compositions according to the present invention.

Particularly preferably the organic polymer is a cellulose ether, e.g. methyl cellulose, hydroxyethylmethylcellulose, or hydroxypropylmethylcellulose (HPMC), for example a Methocel® (available from Colorcon, England) such as Methocel A, Methocel E, Methocel F, Methocel K, Methocel J or Methocel HB or a Metolose® such as Metolose SM, Metolose SH or Metolose SE. Especially preferably the organic polymer is a hydroxypropylmethylcellulose, e.g. from 5 cps Methocel E to 15000 cps Methocel K15M.

Even very small quantities of the organic polymer serve to achieve a beneficial effect in the compositions of the invention. Thus in the compositions of the invention the organic polymer is conveniently present at 0.05 to 35% by weight, preferably 0.1 to 20%, more preferably 0.5 to 15%, and most preferably 2 to 11% by weight (relative to the total weight of drug compound, acid, cyclodextrin and organic polymer). The content and viscosity grade of the organic polymer both affect the dissolution profile for the drug compound in the compositions of the invention, with increased organic polymer content and/or increased viscosity grade (e.g. 15000 mPa.s in place of 5 mPa.s (mPa.s values being at 2% aqueous solution at 20°)) both tending to decelerate drug compound dissolution). Accordingly the selection of the identity and quantity of the organic polymer will generally depend upon the dissolution profile that is desired. For example, a composition that provides sustained release of the drug, will comprise a water soluble polymer having an apparent viscosity of more than 1,000 mPa.s when dissolved in a 2% aqueous solution at 20°C.

The drug compound used in the compositions of the invention may be any organic or inorganic material which is no more than sparingly soluble, *i.e.* which is sparingly soluble, slightly soluble, very slightly soluble, or practically insoluble in pure water at 21°C (ie. requiring from 30, from 100, from 1000 or from 10000 parts water to put 1 part by weight drug compound into solution). In particular, the drug is a basic

compound.

Examples of such poorly water-soluble compounds that may be used in the compositions of the invention include nifedipine, itraconazole (described in EP-A-6711), saperconazole (see US-A-4916134), (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (Compound 40 in WO96/13499), cisapride (described in EP-A-76530), (B)-N-[4-[2-ethyl-1-(1H-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzothiazolamine (described in WO-97/49704); methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b][3]benzazepine-3-carboxylate (described in WO-97/34897);
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile (described in EP-0,834,507);
(B-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;
(2S-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;
3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridin-2(1*H*)-yl]ethyl]-2-methyl-4*H*-pyrido-[1,2-a]pyrimidin-4-one;
N-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-2-benzothiazolamine;
(B1)-*N*-[4-[2-(dimethylamino)-1-(1*H*-imidazol-1-yl)propyl]phenyl]-2-benzothiazolamine (described in WO-97/49704)
(B)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
(B)-*N*-[4-[2-ethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzothiazolamine;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N*,*N*-dipropylpyrazolo[2,3-a]-pyrimidin-7-amine monohydrochloride;
(S)-[1-[2-[3-[(2,3-dihydro-1*H*-inden-2-yl)oxy]-4-methoxyphenyl]propyl]-1*H*-imidazol-2-yl]cyanamide; and
(+)-(B-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazineacetamide (S)-hydroxybutanedioate (1:1).

Further suitable active ingredients are those which exert a local physiological effect, as well as those which exert a systemic effect, either after penetrating the mucosa or - in

the case of oral administration - after transport to the gastro-intestinal tract with saliva. The dosage forms prepared from the compositions according to the present invention are particularly suitable for active ingredients which exert their activity during an extended period of time, i.e. drugs having a half-life of at least several hours.

Examples thereof are :

analgesic and anti-inflammatory drugs (celecoxib, MK966, L-745,337, NSAIDs, fentanyl, indomethacin, ketoprofen, nabumetone, oxyphenbutazone, paracetamol, phenylbutazone, piroxicam, tramadol) ; anti-arrhythmic drugs (gallopamil, procainamide, quinidine, verapamil) ; antibacterial and antiprotozoal agents (amoxicillin, ampicillin, benzathine penicillin, benzylpenicillin, cefaclor, cefadroxil, cefprozil, cefuroxime axetil, cephalexin, chloramphenicol, chloroquine, ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxyxycline, erythromycin, flucloxacillin, halofantrine, isoniazid, kanamycin, lincomycin, mefloquine, minocycline, nafcillin, neomycin, norfloxacin, ofloxacin, oxacillin, phenoxymethyl-penicillin, pyrimethamine-sulfadoxime, quinine, streptomycin); anti-coagulants (warfarin) ; antidepressants (amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dothiepin, doxepin, fluoxetine, fluvoxamine, gepirone, imipramine, lithium carbonate, mianserin, milnacipran, nortriptyline, paroxetine, sertraline ; 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridin-2(1*H*)-yl]ethyl]-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one) ; anti-diabetic drugs (glibenclamide, metformin) ; antiepileptic drugs (carbamazepine, clonazepam, ethosuximide, phenobarbitone, phenytoin, primidone, topiramate, valpromide) ; antifungal agents (amphotericin, clotrimazole, econazole, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole nitrate, nystatin, terbinafine, voriconazole) ; antigout (benzbromarone, probenecid) ; antihistamines (astemizole, cinnarizine, cyproheptadine, decarboethoxyloratadine, fexofenadine, flunarizine, levocabastine, loratadine, norastemizole, oxatomide, promethazine, terfenadine) ; anti-hypertensive drugs (captopril, clonidine, cyclizine, diazoxide, dihydralazine, enalapril, fosinopril, guanethidine, ketanserin, lisinopril, minoxidil, prazosin, ramipril, rescinnamine, reserpine, terazosin) ; anti-muscarinic agents (atropine sulphate, hyoscine) ; antivirals (acyclovir, AZT, ddC, ddI, ganciclovir, loviride, tivirapine, 3TC, delavirdine, indinavir, nelfinavir, ritonavir, saquinavir) ; antineoplastic agents and antimetabolites (adriamycine, cladribine, dactinomycin, daunorubicin, doxorubicin, etoposide, mitomycin, mitoxantrone, paclitaxel, taxol, taxotere, trimetrexate, vincristine, vinblastine) ; anti-migraine drugs (alniditan, naratriptan, sumatriptan) ; anti-Parkinsonian drugs (bromocryptine mesylate, carbidopa, levodopa, selegiline) ; antipsychotic, hypnotic, anxiolytic and sedating agents (alprazolam, buspirone,

chlordiazepoxide, chlorpromazine, chlorprothixene, clozapine, diazepam, flupenthixol, fluphenazine, flurazepam, haloperidol, 9-hydroxyrisperidone, lorazepam, mazapertine, melperone, methaqualone, olanzapine, oxazepam, pimozide, pipamperone, piracetam, promazine, risperidone, selfotel, seroquel, sertindole, sulpiride, temazepam, thioridazine, thiothixene, triazolam, trifluoperazine, trifluperidol, triflupromazine, ziprasidone, zolpidem) ; anti-stroke agents (lubeluzole, lubeluzole oxide, riluzole, aptiganel, eliprodil, remacemide) ; antitussive (dextromethorphan, laevodropropizine, noscapine) ; beta-adrenoceptor blocking agents (atenolol, bupranolol, carvedilol, labetalol, metipranolol, metoprolol, nebivolol, oxprenolol, propanolol) ; cardiac inotropic agents (amrinone, digitoxin, digoxin, milrinone) ; corticosteroids (beclomethasone dipropionate, betamethasone, budesonide, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone) ; disinfectants (chlorhexidine) ; diuretics (acetazolamide, amiloride, benzthiazide, chlorothiazide, chlorthalidone, dichlorphenamide, ethacrynic acid, ethoxzolamide, frusemide, hydrochlorothiazide, hydroflumethiazide, isosorbide, polythiazide, spironolactone, triamterene, trichloromethiazide) ; enzymes ; ergot alkaloids (codergocrine, ergotamine, nicergolin) ; essential oils (anethole, anise oil, caraway, cardamom, cassia oil, cineole, cinnamon oil, clove oil, coriander oil, dementholised mint oil, dill oil, eucalyptus oil, eugenol, ginger, lemon oil, mustard oil, neroli oil, nutmeg oil, orange oil, peppermint, sage, spearmint, terpineol, thyme) ; gastro-intestinal agents (bromopride, cimetidine, cisapride, clebopride, diphenoxylate, domperidone, famotidine, lansoprazole, loperamide, loperamide oxide, mesalazine, metoclopramide, mosapride, nizatidine, norcisapride, olsalazine, omeprazole, pantoprazole, perprazole, pirenzepine, prucalopride, ranitidine, rabeprazole, ridogrel, sulphasalazine) ; haemostatics (aminocaproic acid) ; immunosuppressants (cyclosporin A, tacrolimus) ; lipid regulating agents (atorvastatin, lovastatin, pravastatin, probucol, simvastatin) ; local anaesthetics (benzocaine, lignocaine) ; opioid analgesics (buprenorphine, codeine, dextromoramide, dextropropoxyphene, dihydrocodeine, hydrocodone, oxycodone, morphine, papaverine, pentazocine, pethidine) ; parasympathomimetics (eptastigmine, galanthamine, metrifonate, neostigmine, physostigmine, tacrine, donepezil, rivastigmine, milameline, sabcomeline, talsaclidine, xanomeline, memantine, lazabemide) ; sex hormones (androgens : methyltestosterone, oxymetholone, stanozolol ; oestrogens : conjugated oestrogens, ethinyloestradiol, mestranol, oestradiol, oestriol, oestrone ; progestogens ; chlormadinone acetate, cyproterone acetate, 17-deacetyl norgestimate, desogestrel, dienogest, dydrogesterone, ethynodiol diacetate, gestodene, 3-keto desogestrel, levonorgestrel, lynestrenol, medroxy-progesterone acetate, megestrol, norethindrone, norethindrone acetate,

norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, progesterone, quingestanol acetate) ; stimulating agents (sildenafil) ; sympathomimetics (ephedrine, clenbuterol, fenoterol, norfenefrine, pseudoephedrine) ; vasodilators (amlodipine, amyl nitrite, buflomedil, buphenine, carbocromen, diltiazem, dipyridamole, glyceryl trinitrate, isosorbide dinitrate, lidoflazine, molsidomine, nicardipine, nifedipine, nimodipine, oxpentifylline, pentaerythritol tetranitrate).

Other examples include the following:

alpha-Lipoic acid	lactose	methylxanthine
8-Methoxypsoralen	lithium salts	phytomenadione
Allopurinol	magnesium salts	propylthiouracil
alpha.-Tocopherol	menadione	
iron salts	methylthiouracil	

Drug compounds suitable for use in the compositions of the invention include drugs of all types conventionally administered topically (e.g. in a gel patch) or into an externally voiding body duct, e.g. orally, nasally, aurally, rectally or vaginally. Such drugs include in particular antifungals, calcium channel blockers, antibacterials, antihypertensives, antivirals, analgesics, apolipoprotein B synthesis inhibitors, and drugs which modify transit of gi tract contents (e.g. antidiarrhoea agents or motility promoters). Indeed, the invention is particularly applicable to poorly water-soluble imidazole, triazole, imidazo-benzazepines, nitrophenyl-pyridine, *N*,*N*'-bisphenyl-piperazine, and *N*-phenoxyalkyl-piperidine derivatives, e.g. the compounds mentioned above and compounds as described in EP-A-6711, WO96/13499 and EP-A-76530.

The compositions of the invention may conveniently contain the drug compound at 0.001 to 50% by weight, preferably 0.1 to 35%, more preferably 0.5 to 30%, especially 8 to 25% and most especially 10 to 15% by weight (relative to the total weight of acid, cyclodextrin, organic polymer and drug compound). The quantity of drug will of course depend upon the desired dissolution profile, the intrinsic solubility of the drug compound and the drug dosage required where the drug is to be delivered in dosage units (e.g. capsules, coated tablets, etc).

Thus the present invention also provides pharmaceutical dosage forms comprising a therapeutically effective amount of a composition as described hereinbefore.

For example if the drug is to be delivered in a standard capsule (e.g. with a 900 mg capacity for a glass thermoplastic system as described in the Examples hereto, and the desired drug dose is 100 mg/capsule) then the quantities and natures of the other composition components may be selected to give the desired drug dissolution profile - in general only a small quantity of organic polymer, e.g. 20 to 50 mg, may be necessary, and the balance may be made up from acid and cyclodextrin with the ratio of acid to cyclodextrin being set according to the required dissolution profile, e.g. with 200 to 400 mg cyclodextrin and 450 to 650 mg acid.

Besides the drug compound, the organic polymer, the acid and the cyclodextrin, the compositions of the invention may contain other conventional pharmaceutical excipients, e.g. flavours, colouring agents, antioxidants, bulking agents, fats, waxes, coating agents, dispersants, suspension fluids (e.g. where the composition coated with a gastric juice resistant coating and dispersed as particles in a suspension fluid such as water or a syrup), etc. Preferably such components when in intimate admixture with the drug compound will make up only a minor proportion of the composition, e.g. 0.01 to 10% by weight (relative to the total weight of acid, organic polymer, cyclodextrin and drug compound). However where the composition of the invention is encapsulated or disposed in a carrier (e.g. a fluid or a solid or semi-solid matrix), the further components not in intimate admixture with the drug compound (e.g. coating or encapsulating materials, dispersion media, etc.) may of course make up a minor or major proportion, e.g. 5 to 95% by weight, of the overall composition.

The compositions of the invention may be prepared by making an intimate admixture of the drug compound, cyclodextrin, acid and organic polymer. This may be effected most straightforwardly by dissolving these components in a liquid solvent therefor and subsequently removing the solvent. Thus viewed from a further aspect the invention provides a process for the preparation of a pharmaceutical composition, said process comprising: dissolving a drug compound, a water-soluble cyclodextrin, a physiologically tolerable water-soluble acid and a physiologically tolerable water-soluble organic polymer in a solvent; removing solvent from the resultant solution; optionally forming the resultant product into desired shapes; and optionally coating the resulting product with a physiologically tolerable coating material.

The solvent used in the process of the invention is preferably a physiologically tolerable material, suitably an organic solvent such as a C_{1-6} alkanol (e.g. ethanol), acetone, DMF, a linear or cyclic ether (e.g. diethyl ether, dimethyl ether, or THF), cyclohexane, DMSO,

etc. or a solvent mixture that also may comprise water. For an acid with a high melting point, solvents or solvent mixtures which have high boiling points may conveniently be used; generally however the boiling point of the solvent or solvent system will be no more than about 100°C. Such solvents may be used efficiently in the production of the compositions of the invention and the level of residual solvent will be minimal. The solvent may conveniently be removed by evaporation, e.g. under reduced pressure, and as this may leave some solvent residue (e.g. up to 3% by weight) it is particularly desirable to use a solvent such as ethanol (or an ethanol-water mixture) which is a permitted pharmaceutical excipient.

If the drug compound is insoluble or poorly soluble in the solvent of choice, the process of the invention may involve dispersion of microparticles (e.g. nanoparticles having a particle size of 1 to 100 nm) of the drug compound in the solvent rather than full dissolution of the drug compound. If this is done, it is desirable that the drug compound particles be as small as possible. Nanoparticles of insoluble compounds may be prepared for example by various precipitation techniques or by milling with physiologically tolerable inorganic beads, e.g. of zirconia (EP-0,499,299).

The solvent removal may be essentially complete or it may be incomplete, in the former case to produce a solid or a gel-like solid or semi-solid, and in the latter case to produce a viscous fluid which can for example be filled into capsules.

In general, essentially complete solvent removal will be preferred as the resultant product can then readily be shaped. Shaping may be effected by spray-drying the solution (to provide the product in particulate form), by evaporation of solvent from solution disposed in molds, by molding (e.g. injection molding), by extrusion and the like. In general the product can be formed when hot and allowed to solidify on cooling. The shaped product may likewise be produced in film or sheet form by evaporation or by pouring a heated mass onto a plate and evaporating off the solvent.

In one preferred embodiment the product is shaped by filling into (e.g. by pouring or by extrusion) capsule shells, e.g. of gelatin.

The product may be hygroscopic, and thus may be "tacky" if touched by hand due to its absorption of moisture from the skin. Accordingly it is particularly preferred for the product to be provided with a protective coating to prevent moisture uptake during handling. Such coatings may for example take the form of capsule casings (as described above), tablet coatings, protective film or web coatings, and moisture-proof removable

wrappings. Tablet coatings may be applied in conventional manner and may be such as to dissolve in the mouth or stomach (e.g. sugar or sugar/beeswax coatings), or alternatively may be gastric juice resistant polymers (such as the gastric juice resistant Eudragit® coatings produced by Röhm GmbH) where it is desired that drug uptake should occur in the intestines. Protective films or webs may for example be used where the product is to be applied topically, e.g. for uptake across the skin or a toe or finger nail. In this event a pad of the composition will generally be disposed between an adhesive upper protective layer and a lower removable layer. An example of a topical application form for application on nails and adjoining tissue, e.g. for the treatment of fungal infection, is shown in US-A-5181914.

Where the product is produced in particulate form, e.g. by spray-drying, the particles can be loaded into water-tight administration devices (e.g. spray devices or powder dosing devices such as inhalers) for oral, nasal or topical administration of the particulate. Alternatively particulates may be loaded into capsules or mixed with bulking agents such as lactose, starch, microcrystalline cellulose and mixtures thereof, and compressed to form tablets. In any event, the particles may additionally be provided with one or more coatings, e.g. to provide a delayed or prolonged release administration forms.

Generally however it will be preferred to shape the product into individual doses and to provide these with a protective coat, e.g. to produce a capsule, coated tablet or film covered pad single dosage unit.

While not wishing to be bound by theory it is thought that the advantageous drug compound dissolution profile for the compositions of the invention is achieved as a result of a combination of the effects of the components of the composition on exposure to water or aqueous body fluids. The water and the acid provide a highly acidic microenvironment in which the solubility of the drug compound is increased. This acidic microenvironment contains the cyclodextrin which is capable of complexing the solubilized drug causing the production of a supersaturated solution of the drug compound and this supersaturated solution is stabilized by the viscosity enhancing effects of the organic polymer which hinders precipitation of the drug as the pH increases as the microenvironment becomes more dilute as more water enters.

Accordingly, in the compositions of the invention, in place of the cyclodextrin it is considered possible to use other compounds capable of complexing the drug compound, in particular host complexants capable (like cyclodextrin) of producing host:guest

complexes with the drug compound may be used. Likewise, for base solubilized drug compounds, a physiologically tolerable water-soluble base (e.g. an inorganic or organic base such as an alkali metal carbonate (eg. sodium carbonate) ethanolamine, diethanolamine, etc.) may be used in place of the acid, and in place of the organic polymer a water-soluble physiologically tolerable macromolecular (e.g. of molecular weight ≥ 1kD) viscosity enhancer may be used; in each case in the quantities specified above for the cyclodextrin, acid and organic polymer respectively.

While the benefits of the compositions of the invention are most pronounced where the drug compound is no more than sparingly soluble, the drug dissolution profiles achievable using the combination of drug, cyclodextrin and acid (or base) are such that particularly improved drug uptake profiles may be achieved even where the drug compound is more soluble. Thus viewed from an alternative aspect the invention provides a pharmaceutical composition comprising in intimate admixture a drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

Moreover, where appropriate quantities of cyclodextrin, acid and drug compound are used, it is possible to achieve particularly desirable drug dissolution profiles where the organic polymer is used in very small quantities or even omitted. Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising in admixture a no more than sparingly water soluble organic drug compound, a water-soluble physiologically tolerable organic acid and a water-soluble physiologically tolerable cyclodextrin, said acid and cyclodextrin being present at 1.5 to 15 (preferably 2 to 10, more preferably 2.5 to 6) parts by weight and 1 to 7 (preferably 1.1 to 5, more preferably 1.25 to 4) parts by weight respectively per part by weight of said drug compound.

As has been mentioned above, the compositions according to the invention can be produced with particularly favourable drug dissolution profiles. Thus dissolution may be sufficiently rapid to ensure substantially complete availability of the drug compound for biological uptake (e.g. from the mouth, nose, stomach or vagina) yet sufficiently slow to provide a more prolonged plasma uptake profile (see for example Figure 1 of the accompanying drawings) e.g. by avoidance of drug reprecipitation before the composition reaches the stomach.

Such a dissolution profile is thus novel and advantageous in its own right and viewed from a further aspect the invention provides a pharmaceutical composition comprising

an organic drug compound and at least one water-soluble physiologically tolerable excipient, characterised in that at 5, 15 and 45 minutes after addition of a quantity of said composition containing 100 mg of said drug compound to 600 mL of 0.1N hydrochloric acid at 37°C, from 7 to 25 (preferably 10 to 20, especially 12 to 18) %, 45 to 70 (preferably 50 to 65, especially 54 to 63) % and at least 96 (preferably at least 97, especially at least 98) % respectively of said drug compound is in solution in said hydrochloric acid. These figures relate to *in vitro* dissolution studies conducted in accordance with the monograph USP 23, <711> Dissolution, pp. 1791-1793.

For example, in determining the dissolution profiles set out above, the composition is placed without a coating or with a rapidly soluble coating (e.g. a gelatin capsule shell) in 0.1 N HCl (or an other appropriate medium) and the mixture is stirred using the USP-method with a paddle, apparatus 2, at a speed of 50 or 100 rpm.

The compositions according to the invention may be in any form convenient for topical administration or administration into an externally voiding body cavity (e.g. nose, lungs, mouth, ear, stomach, rectum or vagina). Typical administration forms include patches, tablets, buccal tablets, lozenges, ear-plugs, nose plugs, coated tablets, capsules, suppositories, chewing gum, gels, powders, granules, syrups and dispersions, although patches and powders and more especially capsules and coated tablets are preferred. The drug dosage will depend upon the drug compound as well as the species and size of the subject being treated. Typically, dosages will be 0.5 to 1.2, preferably 0.8 to 1.05 times the conventional dosages for the selected drug compound administered by the same route.

Further, this invention comprioses a pharmaceutical composition or a pharmaceutical dosage form as described hereinbefore for use in a method of therapy or diagnosis of the human or non-human animal body.

This invention also relates to a pharmaceutical composition for use in the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

Or, in other words, the present invention also concerns the se of a pharmaceutical composition as described hereinbefore for the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said

dosage form can be administered at any time of the day independently of the food taken in by said mammal.

This invention also relates to a method of therapy or diagnosis of the human or non-human animal body which comprises administering to said body a therapeutically or diagnostically effective dose of a pharmaceutical composition according to any one of claims 1 to 12.

This invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as claimed in any one of claims 12 to 17, and associated with said package written matter non-limited as to whether the dosage form can be administered with or without food.

The invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings, in which:

Figures 1 and 2 are graphs showing plasma concentrations of the drug (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one administered in a composition according to the invention and in a conventional administration form (sugar particles coated with the drug and loaded in a gelatin capsule) [see Example 6 for further details]; and

Figure 3 is a dissolution profile for the three itraconazole compositions of Example 2.

Example 1

Glass thermoplastic system composition preparation

The following ingredients are mixed in a 250 mL glass flask:

Drug compound (e.g. itraconazole)	20 g
Citric acid monohydrate	100 g

Anhydrous ethanol (100 mL) is added. The glass flask is placed on a steam bath (bain marie) and stirred at 70°C until the drug and acid are completely dissolved (about 10 minutes). Thereafter the following ingredients are added:

Hydroxypropyl-β-cyclodextrin	50 g
Hydroxypropylmethylcellulose (2910.5 mPa.s)	10 g

The flask is placed on the steam bath and stirred at 70°C until dissolution is complete

(about 70 minutes). The solution is then poured onto cleaned stainless steel plates which are then placed in a drying oven for 2 hours at 80°C under vacuum and subsequently for 40°C under vacuum overnight. The plates are then heated to 80°C and the gel residue is scraped off and filled into 900 mg capacity gelatin capsules (size no. 0).

Example 2

Composition preparation

Analogously to Example 1, gelatin capsules having the following relative weights of components are prepared:

(A)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	275 mg	hydroxypropyl-β-cyclodextrin
	25 mg	Methocel E5
(B)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5
(C)	100 mg	Itraconazole
	500 mg	citric acid monohydrate
	225 mg	hydroxypropyl-β-cyclodextrin
	75 mg	Methocel E5
(D)*	200 mg	Methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b]-[3]benzazepine 3-carboxylate
	650 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
(E)	100 mg	(-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one
	500 mg	citric acid monohydrate
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	Methocel E5

* For example 2(D) the composition is loaded into 1100 mg gelatin capsules.

The dissolution profiles of the gels of Example 2(A), (B) and (C) are shown in Figure 3 of the accompanying drawings. These were determined by placing one capsule containing 100 mg of itraconazole in 300 mL of stirred 0.1 N HCl at 37°C and observing the percentage of dissolved drug compound at times 0, 5, 15, 30, 45 and 60 minutes (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm). For Example 2(E), with 100 mg drug compound added to 600 mL of 0.1 N HCl at 37°C, the mean percentages of drug compound in solution at 5, 15, 30 and 45 minutes were 17.22, 61.18, 92.73 and 98.67 respectively (stirring was effected using the USP-method with paddle, apparatus 2, 100 rpm).

The dissolution profile of Example 2(E) was compared with that of a conventional capsule dosage form in which the gelatin capsule is loaded with sugar particles coated with 100 mg of (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one. The capsules were placed in 10 ml of 0.1 N HCl at 37°C in glass vials and shaken in a mechanical shaker (100 strokes per minute) and the percentage of drug compound in solution after 0, 30 and 60 minutes was determined. The results are set out in Table 1 below.

Table 1

	Percentage of drug compound in solution	
Time	Example 2(E)	Conventional Capsule
0	0	0
30	91.26	15.54
60	101.90	18.39

This clearly shows how much more readily the drug compound is made bioavailable by the compositions of the invention.

Example 3

Effect of organic polymer on supersaturation stability

Aqueous solutions of hydroxypropyl-β-cyclodextrin (HPβCD) and Methocel E5 in 300 ml 0.1 N HCl at 37°C were prepared having the concentrations set out in Table 2. The solutions were stirred using the USP-method with paddle, apparatus 2, 150 rpm.

Sample	HPβCD (mg)	Methocel E5 (mg)
1	250	250
2	500	0
3	250	00
4	500	500
5	0	250
6	500	250
7	0	0
8	250	0
9	0	500

To these solutions, with stirring, a concentrated solution of itraconazole in DMF (50 mg/mL) was added dropwise until precipitation was observed. Subsequently the concentration of dissolved itraconazole expressed in mg% (ie. the number of mg dissolved in 100 mL) was observed at 0, 30, 60 and 120 minutes. The results are set out in Table 3 below:

Table 3

Percentage of drug compound in solution

Sample	1	2	3	4	5	6	7	8	9
Time (minutes)									
0	59.52	72.10	58.95	75.47	42.65	75.27	42.60	60.95	42.95
30	62.02	74.40	62.05	78.12	44.85	80.17	44.10	62.92	45.20
60	62.52	70.37	62.50	79.47	45.40	80.40	44.97	64.07	46.00
120	62.79	45.82	63.90	80.77	46.55	81.25	31.32	33.65	47.05
HPBCD: Methocel ratio	1:1	2:0	1:2	2:2	0:1	2:1	0:0	1:0	0:2

These results clearly demonstrate (i) the solubilizing effect of the cyclodextrin (Samples 2, 6 and 4 show the highest initial itraconazole concentrations, followed by Samples 8, 1 and 3, with Samples 7, 5 and 9 showing the lowest initial concentrations) and (ii) the stabilizing effect of the organic polymer (Samples 2, 8 and 7 show the greatest drop in itraconazole concentrations over 120 minutes, etc).

Example 4

Extended release formulation

Analogously to Example 1, gelatin capsules were prepared containing the following:

41.55 mg	Cisapride
508.45 mg	citric acid monohydrate
250 mg	hydroxypropyl-β-cyclodextrin
100 mg	Methocel K15M

This formulation has a much slower dissolution rate than the compositions of Example 2. However the rate of dissolution is much more close to linear with time and shows much less dependence on the pH of the dissolution medium.

Example 5

Nail gel

A gel for application to nails or hooves to effect antifungal treatment is made with the following composition:

Itraconazole	250 mg
Citric acid monohydrate	2083 mg
Hydroxypropyl-β-cyclodextrin	333 mg
Hydroxypropylmethylcellulose (Methocel E5)	83 mg
Anhydrous ethanol	2 ml

Example 6

Body uptake

The plasma concentrations of R 103757 were determined in healthy humans at 0, ½, 1, 1½, 2, 3, 4, 6, 8 and 12 hours after oral administration of 100 mg (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)-thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one as (i) a 5 mg/mL oral solution containing 25% hydroxypropyl-β-cyclodextrin solution administered under fasting conditions, (ii) a conventional capsule containing (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one coated onto sugar particles administered under fasting conditions, (iii) a conventional capsule containing (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one coated onto sugar particles administered after a standard breakfast, (iv) a capsule according to Example 2(E) administered under fasting conditions and (v) a capsule according to Example 2(E) administered after a standard breakfast.

The "standard breakfast" comprised four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of coffee or tea with milk and/or sugar if desired. The 100 mg dose of (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl]-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one was administered just after such a breakfast.

Blood samples of 10 mL were taken to obtain 5 mL plasma. The blood samples were taken, collected in heparinized tubes, and centrifuged at 1000g for 10 minutes within 2 hours of collection. Plasma was transferred into plastic tubes, which were sealed and stored at -70°C until assayed.

The results are shown in Figures 1 and 2 which presents drug concentrations as a function of time. As can be seen, the conventional capsule performs significantly worse than the solution even with fasting. However the capsule according to the invention outperforms the solution after 3 hours whether or not the recipient has fasted and, most surprisingly, completely outperforms the solution where the recipient has not fasted.

Example 7

Effect of pH on dissolution rate

Following the procedure of Example 1, a placebo capsule comprising methylene blue (2,63 mg), citric acid (600 mg), hydroxypropyl-β-cyclodextrin (250 mg) and hydroxypropylmethylcellulose (Methocel E5, 50 mg) was prepared. The dissolution of these capsules was determinated at various pH values according to the USP method (600 ml medium, 37°C, Apparatus 2 with paddle, 100 rpm). The six media tested were : 0.1N HCl (pH 1.55), 0.01N HCl (pH 2.25), 0.001N HCl (pH 2.75), USP pH 4.5 (pH 4.40), USP pH 6.5 (pH 5.80) and USP pH 7.5 (pH 7.0).

The results are set out in **table 4** below :

Time (min.)	0.1N HCl	0.01N HCl	0.001N HCl	USP pH 4.5	USP pH 6.5	USP pH 7.5
0	0.00	0.00	0.00	0.00	0.00	0.00
5	16.62	21.85	16.62	21.40	15.48	16.62
15	60.77	73.75	74.43	71.93	60.55	62.59
30	95.60	104.25	104.93	100.15	102.20	100.83
45	100.83	104.93	105.39	104.48	103.57	104.25
60	102.43	104.70	104.93	105.16	104.48	104.02
pH	1.55	2.25	2.75	4.40	5.80	7.00

Example 8

Following the procedure of Example 1, various drug containing capsules were made having the following relative weights of components :

A. 100 mg itraconazole
500 mg citric acid
250 mg hydroxypropyl-β-cyclodextrin
50 mg HPMC E5

B. 200 mg methyl 6,11-dihydro-11-[1-[2-[4-(2-quinolinylmethoxy)phenyl]ethyl]-4-piperidinylidene]-5*H*-imidazo[2,1-b][3]benzazepine-3-carboxylate
650 mg citric acid
250 mg hydroxypropyl-β-cyclodextrin

C. 100 mg (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one
500 mg citric acid
250 mg hydroxypropyl-β-cyclodextrin
50 mg HPMC E5

D. 100 mg 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]-benzonitrile
500 mg citric acid
250 mg hydroxypropyl-β-cyclodextrin
50 mg HPMC E5

E. 5 mg (B)-N-[4-[2-ethyl-1-(1H-1,2,4-triazol-1-yl)butyl]phenyl]-2-benzo-

		thiazolamine
	500 mg	citric acid
	395 mg	hydroxypropyl-β-cyclodextrin
F.	100 mg	(B-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone
	500 mg	citric acid
	250 mg	hydroxypropyl-β-cyclodextrin
	50 mg	HPMC E5

The dissolution of these compositions was determined according to the USP method (600 ml 0.1 N HCl, 37°C, Apparatus 2 with paddle, 100 ppm), except formulation (A) where only 300 ml medium was used. The results are set out in the following tables 5-10 :

Table 5 : Formulation (A)

Time (min)	sample 1	sample 2	sample 3
0	0.00	0.00	0.00
5	10.75	9.99	10.69
15	56.61	57.18	59.61
30	85.89	88.98	90.24
45	95.46	99.84	96.87
60	101.94	102.06	102.87

Table 6 : Formulation (B)

Time (min)	0.1N HCl	0.01N HCl	0.001N HCl
0	0.00	0.00	0.00
5	27.00	25.17	21.39
15	92.13	86.94	84.75
30	97.11	96.63	93.09
45	98.64	99.45	94.83
60	100.29	100.08	95.28

Table 7 : Formulation (C)

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	13.81	17.28	17.67	19.79	18.56	16.19	17.22
15	58.44	59.10	66.60	63.42	62.46	57.06	61.18
30	92.34	92.94	93.36	92.46	92.52	92.76	92.73
45	98.28	98.94	98.82	99.30	98.52	98.16	98.67
60	100.08	99.54	99.66	100.20	100.02	99.96	99.91

Table 8 : Formulation (D)

	Calculated concentration in % of the active dose
Time (min)	Sample 1
5	0.00
5	7.41
15	49.49
30	86.92
45	99.57
60	99.84
90	101.77
120	103.52
150	103.70

Table 9 : Formulation (E)

	Calculated concentration in % of the active dose		
Time (min)	0.1N HCl	0.01N HCl	0.001 N HCl
0	0.00	0.00	0.00
5	48.72	26.16	24.96
15	100.92	96.36	94.20
30	102.48	98.76	95.76
45	103.08	102.24	96.96
60	102.00	102.00	97.80

Table 10 : Formulation (F)

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	12.66	14.76	12.66	12.66	15.36	17.34	14.24
15	54.36	56.82	61.98	64.80	54.78	63.78	59.42
30	94.26	93.96	97.50	98.40	95.58	97.20	96.15
45	100.98	101.28	100.50	101.16	100.68	101.34	100.99
60	101.22	101.34	101.16	101.52	100.86	101.58	101.28

Example 9

Stability testing of formulation 8 (C)

Capsules of formulation 8(C) were stored for 1 month and 3 months at 40°C, and for 1 year at room temperature. Dissolution measurements were made according to the USP method (600 ml 0.1N HCl, 37°C, paddle apparatus 2,100 rpm).

The following results were obtained :

Table 11 : after 1 month at 40°C

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	10.11	10.79	9.94	9.59	14.35	10.33	10.85
15	59.72	55.02	48.97	54.36	66.54	52.38	56.17
30	93.00	90.06	89.70	92.70	95.46	89.16	91.68
45	100.14	98.22	98.94	99.84	99.48	99.18	99.30
60	100.50	100.92	99.36	99.54	100.56	100.26	100.19

Table 12 : after 3 months at 40°C

	Calculated concentration in % of the active dose						
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	5.74	5.90	13.93	11.49	7.56	7.78	8.73
	43.62	45.00	56.76	48.30	43.14	47.76	47.43
	88.80	89.10	89.70	87.96	84.54	84.42	87.42
	99.36	99.96	99.54	99.78	99.18	100.08	99.65
	100.32	100.14	100.92	100.44	101.70	100.50	100.67

Table 13 : after 1 year at room temperature

	Calculated concentration in % of the active dose			
Time (min)	sample 1	sample 2	sample 3	average
0	0.00	0.00	0.00	0.00
5	14.94	16.14	15.48	15.52
15	61.98	66.12	67.32	65.14
30	92.52	91.86	96.12	93.50
45	99.72	99.60	98.70	99.34
60	101.10	100.80	99.36	100.42

Example 10

Variability in bioavailability of Formulation (D)

The variability in the bioavailability of Formulation (D) in beagle dogs was evaluated as follows. First, two beagle dogs received as single oral administration of a PEG-400 solution comprising 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile at a dose of 10 mg/kg. Plasm levels were measured for 32 hours. After 7 days, the same dogs were now treated with a single oral capsule comprising the formula (D) at 10 mg/kg. Plasm levels were again determined for up to 32 hours after administration. The individual results are as follows.

			Plasma levels (ng/ml)	
Formulation	Day	Time	Dog 1	Dog 2
PEG-400 solution	0	0 h	5.8	NQ
		0.5 h	141	63.2
		1 h	247	158
		2 h	291	141
		4 h	534	200
		6 h	368	171
		8 h	246	141
	1	24 h	95.2	47.4
		32 h	36.1	20.9

			Plasma levels (ng/ml)	
Formulation	Day	Time	Dog 1	Dog 2
GTS capsule	7	0 h	NQ	NA
		0.5 h	24.2	68.5
		1 h	567	600
		2 h	850	859
		4 h	461	492
		6 h	288	343
		8 h	237	207
	8	24 h	74.0	32.9
		32 h	32.7	10.1

NQ : not quantifiable by the HPLC method (< 5.0 ng/ml).

Surprisingly, the plasm levels obtained after administration of the capsules comprising formula (D) are very much more similar to one another in the two test animals than those obtained after administration of the PEG 400 solution.

Example 11

Permeation and accumulation of itraconazole through and in human skin

A Franz cell was fitted with fresh whole human skin and its receptor filled with a 20% (w/v) solution of hydroxypropyl-β-cyclodextrin in water. A Finn Chambers patch was filled with Formulation 8(A) and was then placed on the skin wetted with a small amount of phosphate buffered saline. Samples of the receptor solution were withdrawn at regular intervals and the presence of itraconazole in the solution was measured using high performance liquid chromatography. At no time point could any trace of itraconazole be detected, indicating that this compound did not penetrate whole human skin. At the end of the experiment the skin was thoroughly washed and then extracted in order to determine the amount of itraconazole accumulated in the skin. A mean value of 12.2 $\mu g/cm^2$ could be calculated from the results of 8 independent experiments.

Claims

1. A pharmaceutical composition comprising a no more than sparingly water-soluble drug compound, a cyclodextrin, a physiologically tolerable water-soluble acid, and a physiologically tolerable water-soluble organic polymer.

2. The composition of claim 1 characterised in that the weight ratios of drug compound to acid and of drug compound to cyclodextrin are no more than 2:1.

3. The composition of claim 1 or 2 characterized in that the physical state of said composition is a glass thermoplastic phase.

4. The composition of claim 3 wherein the cyclodextrin is 2-hydroxypropyl-β-cyclodextrin.

5. The composition of claim 3 wherein the acid is selected from the group comprising citric, fumaric, tartaric, maleic, malic, succinic, oxalic, malonic, benzoic, mandelic and ascorbic acid.

6. The composition of claim 5 wherein the acid is citric acid.

7. The composition of claim 3 wherein the polymer is selected from the group comprising
   - alkylcelluloses such as methylcellulose,
   - hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
   - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
   - carboxyalkylcelluloses such as carboxymethylcellulose,
   - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
   - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
   - carboxyalkylcellulose esters,
   - starches,
   - pectins such as sodium carboxymethylamylopectin,
   - chitin derivates such as chitosan,
   - heparin and heparinoids,

- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum and xanthan gum,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

8. The composition of claim 7 wherein the polymer has an apparent viscosity of 1 - 100 mPa.s when dissolved in a 2% aqueous solution at 20°C.

9. The composition of claim 8 wherein the polymer is hydroxypropylmethylcellulose.

10. The composition of claim 3 wherein the drug is a basic compound.

11. A composition according to any one of the preceding claims that dissolves rapidly in body fluids, characterized in that it comprises from 50 to 95 % by weight of acid.

12. A composition according to any one of the preceding claims that provides sustained release of the drug, characterized in that it comprises a water soluble polymer having an apparent viscosity of more than 1,000 mPa.s when dissolved in a 2% aqueous solution at 20°C.

13. A pharmaceutical dosage form comprising a therapeutically effective amount of a pharmaceutical composition as defined in any one of the preceding claims.

14. The dosage form of claim 13 adapted for topical administration or administration into an externally voiding body cavity such as the nose, lungs, mouth, ear, stomach, rectum and vagina.

15. The dosage form of claim 13 wherein said composition is filled into a standard capsule, or alternatively is mixed with bulking agents and compressed into tablets.

16. The dosage form of claim 13, characterised in that at 5, 15 and 45 minutes after

addition of said dosage form to 0.1N hydrochloric acid at 37°C in the dissolution test set forth in USP test <711> in a USP-2 dissolution apparatus equiped with a paddle, from 7 to 25%, 45 to 70% and at least 96% respectively of drug is dissolved in said 0.1 N hydrochloric acid.

17. A pharmaceutical composition according to any one of claims 1 to 12 or a pharmaceutical dosage form according to any one of claims 13 to 17 for use in a method of therapy or diagnosis of the human or non-human animal body.

18. A pharmaceutical composition according to any one of claims 1 to 12 for use in the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

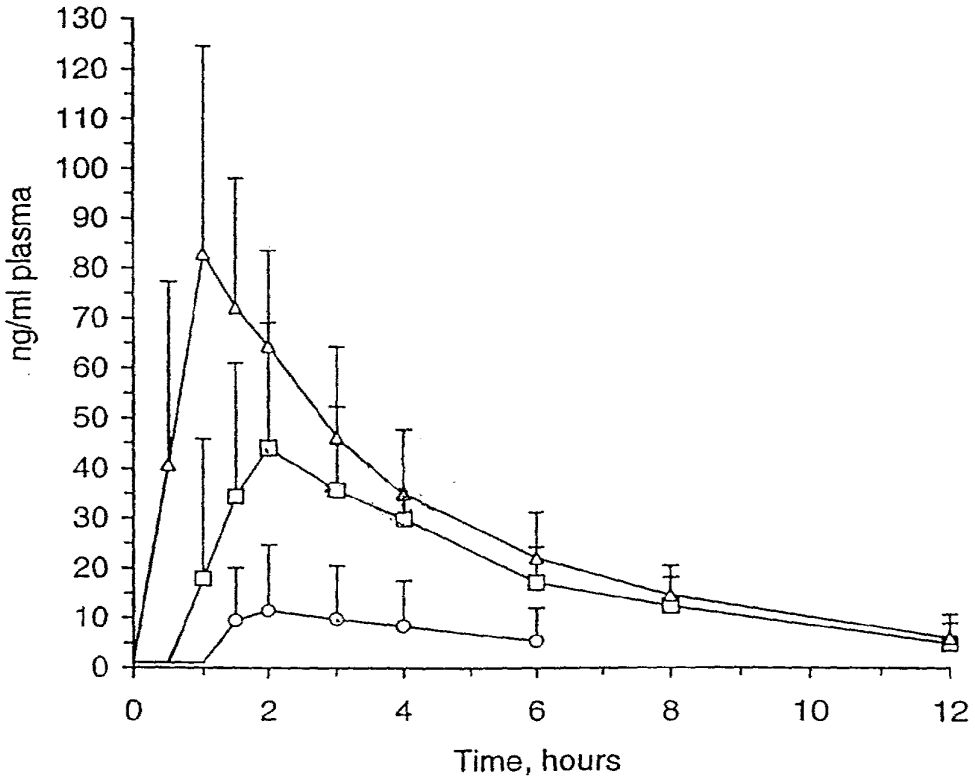
19. Use of a pharmaceutical composition according to any one of claims 1 to 12 for the manufacture of a pharmaceutical dosage form for oral administration to a mammal in need of treatment, characterized in that said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

20. A method of therapy or diagnosis of the human or non-human animal body which comprises administering to said body a therapeutically or diagnostically effective dose of a pharmaceutical composition according to any one of claims 1 to 12.

21. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form as claimed in any one of claims 12 to 17, and associated with said package written matter non-limited as to whether the dosage form can be administered with or without food.

1/3

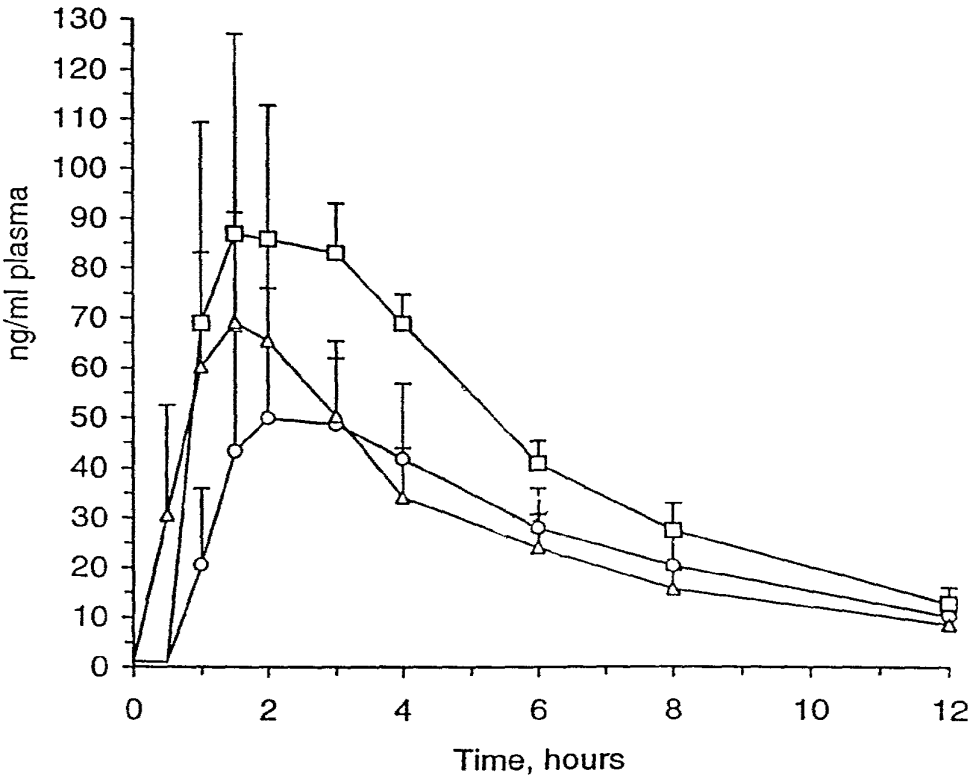
Figure 1



—Δ— treatment (i)
—o— treatment (ii)
—□— treatment (iii)

2/3

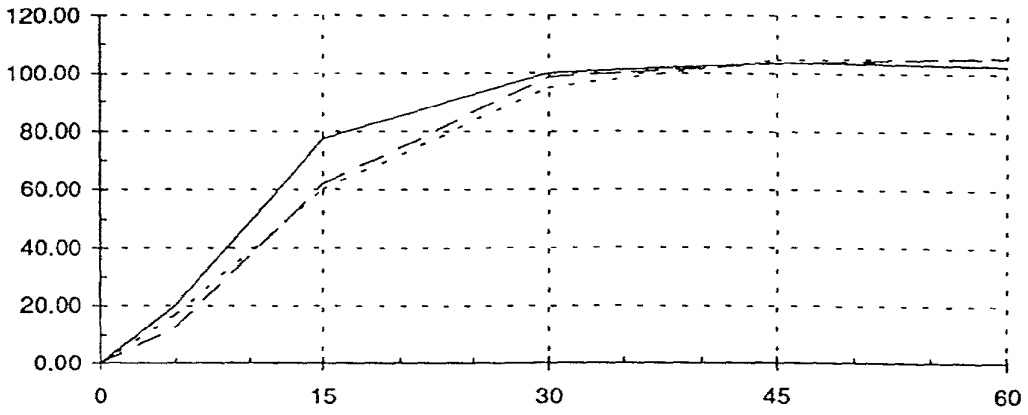
Figure 2



—Δ— treatment (i)
—o— treatment (iv)
—□— treatment (v)

3/3

Figure 3



—— formula 2(A)
– – – formula 2(B)
- - - - formula 2(C)

INTERNATIONAL SEARCH REPORT

Interr ..al Application No
PCT/EP 98/03189

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48 A61K9/14 A61K9/48

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 689 844 A (TECNIMEDE SOCIEDADE TECNICO ME) 3 January 1996 see the whole document ---	1,2,4-8, 10,12, 13,15, 17-21
X,Y	WO 94 12217 A (INSITE VISION INC) 9 June 1994 see the whole document ---	1,2, 4-10,12, 13,15, 17-21
X	WO 90 14082 A (CIRD) 29 November 1990 see the whole document --- -/--	1,2,4, 7-9, 12-14, 17-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 1998	18/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, W

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 98/03189

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 300 526 A (JANSSEN PHARMACEUTICA NV) 25 January 1989 see the whole document	5-7,14, 17-21
Y	WO 97 18245 A (FARMARC NEDERLAND BV ;GLINTENKAMP LUETA ANN (ZA); PENKLER LAWRENCE) 22 May 1997 see the whole document	1,2,4,5, 7,9,13, 14,17-21
A	EP 0 614 666 A (STERLING WINTHROP INC) 14 September 1994	
A	US 5 472 954 A (LOFTSSON THORSTEINN) 5 December 1995	
A	US 4 351 846 A (MIYAKE HAJIMU ET AL) 28 September 1982	
A	US 4 956 351 A (MESENS JEAN L ET AL) 11 September 1990	
A	US 5 206 025 A (COURTEILLE, F. ET AL) 27 April 1993	
A	WO 95 00144 A (HANHIJAERVI HANNU ;LEIRAS OY (FI); OKSALA OLLI (FI); SUHONEN PEKKA) 5 January 1995	
A	EP 0 472 327 A (SENJU PHARMA CO) 26 February 1992	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 98/03189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/03189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0614666 A		NZ 248590 A	26-07-1995
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Electronic Acknowledgement Receipt

EFS ID:	13457908
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Lance Logan
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	09-AUG-2012
Filing Date:	07-JAN-2011
Time Stamp:	14:17:43
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	Information Disclosure Statement (IDS) Form (SB08)	IDS.pdf	819507 91c879bacd3af8d60c8616d1b198aba73d01f89e	no	4

Warnings:	
Information:	**173**

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

2	Foreign Reference	WO9962958A1.pdf	1414115 89f6c06179c66d2454eeffad3fe2e64373c57e3f	no	36
Warnings:					
Information:					
3	Foreign Reference	WO9855148A1.pdf	1986336 dcde016de9bf3453b97622aa85beec9a0860b662	no	42
Warnings:					
Information:					
4	Non Patent Literature	Drugs-in-Japan.pdf	409972 5d22071e7012d1582746081e5d596835723ca228	no	4
Warnings:					
Information:					
5	Non Patent Literature	JPOAwTranslation.pdf	362379 6000e805afa0ccdaa48350addcafec83dc6eb660	no	8
Warnings:					
Information:					
			Total Files Size (in bytes):	4992309	

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

13974 7590 11/08/2012

SNR DENTON US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
11/08/2012	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@snrdenton.com
martin.bruehs@snrdenton.com

Office Action Summary	Application No.	Applicant(s)	
	12/986,310	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- 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 *1* 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 *07 January 2011*.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1-64* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

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

9)☒ Claim(s) *1-64* are subject to restriction and/or election requirement.

Application Papers

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

11)☐ The drawing(s) filed on _____ 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).

12)☐ 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

13)☐ 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: _____.

DETAILED ACTION

This Office Action details a restriction requirement and one election of species requirement.

Restriction Requirement

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8, 25-31, 46-61, drawn to a cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and pharmaceutical compositions comprising thereof, classified in class 536, subclass 27.7.

II. Claims 9-24 and 62-64, drawn to a method for enhancing the oral bioavailability of cladribine or treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to a subject in need thereof a pharmaceutical composition comprising said cladribine-cyclodextrin complex, classified in class 514, subclass 45.

III. Claims 32-45, drawn to a method of making cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b)

amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, classified in class 536, subclass 55.3.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product as claimed can be used in a materially different process of using that product such as an *in vivo* efficacy study of cladribine as a function of solubility.

Inventions I and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product as claimed can be made by another and materially different process such as by melt-extrusion to make a glassy or amorphous material.

Inventions II and III are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the

inventions as claimed have a materially different design, function and effect, as the process of Group II is drawn to treating a subject suffering from a disease or condition by adminstering said cladribine-cyclodextrin complex whereas the process of Group III is drawn to making said cladribine-cyclodextrin complex. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because at least the following reason(s) apply:

(a) the inventions have attained recognition in the art as a separate subject for inventive effort in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, employing different search queries for structural features of a cladribine-cyclodextrin complex, methods of treatment of a subject suffering from a cladribine-responsive condition, or processing conditions for making a cladribine-cyclodextrin complex).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement

may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Election of Species Requirement

If Applicant elects the invention of Group II, Applicant is further required to elect from the following Election of Species.

This application contains claims directed to the following patentably distinct species of cladribine-responsive condition treated. The species are independent or distinct because the different cladribine-responsive conditions treated are characterized by different symptoms and define different patient populations to be treated. In addition, these species are not obvious variants of each other based on the current record.

Examples of cladribine-responsive condition treated are:

a) multiple sclerosis disclosed in claims 19 and 20,

b) rheumatoid arthritis disclosed in claim 19, and

c) leukemia disclosed in claim 19.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 9-19, 21-24 and 62-64 are generic or subgeneric.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

(c) the species require a different field of search (for example, employing different search queries for different cladribine-responsive conditions treated characterized by different symptoms and different patient populations).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) **and**

(ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Due to the complexity of the restriction and species election requirement, no telephone communication was made. See MPEP 812.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all

claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is (571)270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jonathan S Lau/
Examiner, Art Unit 1623

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner
Art Unit 1623

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012								
	37	÷								
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PATENT
Attorney Docket No.: 20009904-0067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nicholas S. BODOR et al.	)	**MAIL STOP AMENDMENT**
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
Filed: January 7, 2011	)	Group Art Unit: 1623
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100

RESPONSE TO RESTRICTION REQUIREMENT

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

Sir:

In response to the Restriction Requirement dated November 8, 2012, Applicants provide the following remarks.

The Examiner has required restriction to one of the following inventions:

Group I	Claims 1-8, 25-31 and 46-61, drawn to a cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and pharmaceutical compositions comprising thereof, classified in class 536, subclass 27.7.;
Group II	Claims 9-24 and 62-64, drawn to a method for enhancing the oral bioavailability of cladribine or treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to a subject in need thereof a pharmaceutical composition comprising said cladribine-cyclodextrin complex, classified in class 51 4, subclass 45; and
Group III	Claims 32-45, drawn to a method of making a cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, classified in class 536, subclass 55.3.

In response to the Office's Restriction Requirement, Applicants elect, *with traverse,* Group I, Claims 1-8, 25-31 and 46-61, drawn to a cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion

complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and pharmaceutical compositions comprising thereof, classified in class 536, subclass 27.7.

In electing the above invention, Applicants reserve the right to request rejoinder under M.P.E.P § 821.04 of process claims that depend from or otherwise include all of the features of an allowable composition claim.

For at least the reasons that follow, Applicants respectfully request reconsideration and withdrawal of the requirement.

For proper restriction between patentably distinct inventions: (1) the inventions must be independent or distinct as claimed; and (2) there would be a serious burden on the Examiner if restriction is not required. See, M.P.E.P. § 803.

Applicants further submit that it is premature to require such restrictions in the absence of having first conducted searches on the claimed inventions to determine the extent of the burden. Absent such searches, it is difficult to maintain that a review of all of the cited claims would be a serious burden on the Examiner. At the very least, such initial searches should be conducted for efficiency purposes so that the searches would not need to be repeated in the event the Applicant was required to file one or more divisional applications. Applicants therefore believe that such a restriction is not required.

Accordingly, for the at least the above reasons, the Requirement for Restriction is improper and should be withdrawn.

For at least these reasons and to avoid duplicate efforts at the Patent Office and undue delay and expense to Applicants, reconsideration and withdrawal of the Restriction Requirement are respectfully requested.

If there are any questions concerning this Response or the application in general, Applicants invite the Examiner to telephone the undersigned at the below-listed number.

Respectfully submitted,

SNR Denton US LLP

Date January 8, 2013

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26,254

Customer No. 13974
202 408 6400

Electronic Patent Application Fee Transmittal

Application Number:	12986310
Filing Date:	07-Jan-2011
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Attorney Docket Number:	20009904-0067

Filed as Large 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 - 1 month with $0 paid	**192** 1251	1	150	150

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**150**

Electronic Acknowledgement Receipt

EFS ID:	14646869
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	08-JAN-2013
Filing Date:	07-JAN-2011
Time Stamp:	18:22:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$150
RAM confirmation Number	5468
Deposit Account	193140
Authorized User	BAUMEISTER, MARY KATHERINE

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)

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 1.20 (Post Issuance 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	Extension of Time	EOT.pdf	57377 f70356080d711c1899930f69b731d4df8e3f0874	no	1
Warnings:					
Information:					
2	Response to Election / Restriction Filed	Response.pdf	112119 12d73a32acd51762c9bb88eb6c1a59de623fd15f	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30461 9763fd0735dc01df125006f28c0af42b22da9504	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	199957		

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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/22 (09-11)
Approved for use through 07/31/2012. OMB 0651-0031
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.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 20009904-0067
Application Number 12/986,310		Filed January 7, 2011
For ORAL FORMULATIONS OF CLADRIBINE		
Art Unit 1623	Examiner Jonathan S. LAU	Confirmation Number 6100

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))	$150	$75	$ 150
☐	Two month (37 CFR 1.17(a)(2))	$570	$285	$ ____
☐	Three month (37 CFR 1.17(a)(3))	$1290	$645	$ ____
☐	Four month (37 CFR 1.17(a)(4))	$2010	$1005	$ ____
☐	Five month (37 CFR 1.17(a)(5))	$2730	$1365	$ ____

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

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

☒ Payment by credit card. Fee being paid concurrent with the filing of this EOT.

☐ 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 **19-3140**.

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 26,254 .
☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. ____

Mary Katherine Baumeister
Signature

January 8, 2013
Date

Mary Katherine Baumeister
Type or printed name

202-408-6400
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____ 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.**

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

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/986,310	01/07/2011	

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	01/08/2013	(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))	* 64	Minus	** 64	= 0	X $ =		OR	X $62=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $250=	0
	☐ 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	0

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:
/ANTHONY WILLIAMS/

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.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

13974 7590 02/25/2013

SNR DENTON US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
02/25/2013	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@snrdenton.com
martin.bruehs@snrdenton.com

Office Action Summary	Application No.	Applicant(s)	
	12/986,310	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- 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 *08 January 2013*.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1-64* is/are pending in the application.

5a) Of the above claim(s) *9-24,32-45 and 62-64* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8,25-31 and 46-61* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☒ The drawing(s) filed on *07 January 2011* 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).

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) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7 Jan 2011, 9 Aug 2012*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

This application is a domestic application, filed 7 Jan 2011; and claims benefit as a CON of 10/551,205, issued as Patent 7,888,328, which is a 371 of PCT/US2004/009387, filed 26 Mar 2004, which claims benefit of provisional application 60/458,922, filed 28 Mar 2003, and claims benefit of provisional application 60/484,756, filed 2 Jul 2003, and claims benefit of provisional application 60/541,247, filed 4 Feb 2004.

Claims 1-64 are pending in the current application. Claims 9-24, 32-45 and 62-64, drawn to non-elected inventions, are withdrawn. Claims 1-8, 25-31 and 46-61 are examined on the merits herein.

However, the parent provisional applications 60/458,922 and 60/484,756 upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the instant claims 1-8, 25-31 and 46-61 of this application since all parent applications are not seen to disclose the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex in the independent claims 1 and 25. Written description for a cladribine freeze-dried cyclodextrin complex may be found in 60/458,922 at page 16-18, and a drug-cyclodextrin complex in a "highest thermodynamic activity state" may be found in 60/484,756 at page 2, paragraph 2 and cladribine-cyclodextrin complex at page 6,

however no support is found for the complex which is said intimate amorphous admixture. Thus, the filing date of the instant claims is deemed to be provisional application 60/541,247, filed 4 Feb 2004. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-8, 25-31 and 46-61 in the reply filed on 8 Jan 2013 is acknowledged. The traversal is on the ground(s) that there is no serious burden to examine the different groups of inventions. This is not found persuasive because while the groups of inventions are related to the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, the search to examine the different groups of inventions would involve different fields such as pharmacokinetics in the treatment of a subject or specific processing conditions to make said complex. Further, while claims 46-61 recite a product-by-process, determination of patentability is based on the product itself and the patentability of a product does not depend on its method of production. Even without having first conducted searches on the claimed invention it is

clear that searching different fields of art, such as the field of pharmacokinetics or processing conditions to make a complex, would constitute a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-24, 32-45 and 62-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8 Jan 2013.

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.

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 1-8, 25-31 and 46-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, provided by Applicant in IDS mailed 7 Jan 2011) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). The disclosed product is substantially identical to the product-by-process. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24). The phrase "one or more cyclodextrin hydroxy groups" combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of "randomly methylated β-cyclodextrins". Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of the instant claims invention. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex. Therefore a

composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a “saturated” complex and meets the limitations of instant claims 2 and 57. Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Baert et al. provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

To address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the equation for the equilibrium of the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state due to the lack of a solvent, the equilibrium and thus equilibrium products, the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex, would still be inherent in the product disclosed by Schultz et al.

Schultz et al. does not specifically disclose the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an

amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and the composition comprising no significant amount of free crystalline cladribine therein (instant claim 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 7). Schultz et al. does not specifically disclose the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 25). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 5 and 29). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 8 and 31). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, implying a cladribine to cyclodextrin ratio of 1:14.38, or the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 55), implying a cladribine to cyclodextrin ratio of 1:10.55.

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of "about" as a variance of 20% provided in the instant specification page 9, lines 6-11. Such a saturated complex would consist of only (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and being a saturated complex corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin disclosed by Schultz et al. in the ratios of cladribine and cyclodextrin taught by Baert et al. One of ordinary skill in the art would be motivated to combine the Schultz et al. and Baert et al. because Schultz et al. incorporates-by-

reference Baert et al. and because Baert et al. suggests that improving a similar product according to the teachings of Baert et al. has beneficial properties such as high bioavailability and dissolution rate (Baert et al. page 7, lines 25-27). One of ordinary skill in the art would have an expectation of success because the ratios taught by Baert et al. fall within the range of ratios that is implicitly disclosed by Schultz et al. Schultz et al. in view of Baert et al. does not teach the specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Baert et al. suggests optimization of the ratio (Baert et al. page 11, lines 1-5). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesireable recrystallization of cladribine in tissue may occur and damage the surround tissue and that complexes with cyclodextrin are known to solubilize the compound (Schultz et al. column 2, lines 1-15). Schultz et al. in view of Baert et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, it is well known in the art that the formation of an inclusion complex from a non-inclusion complex is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin. This molecular

inclusion equilibrium is a process inherent in the formation of the inclusion complex in both aqueous solutions and hot melt liquid mixtures, and Baert et al. teaches variation of the ratio of cladribine to cyclodextrin and hence their relative concentration.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed, namely the position of the equilibrium process governing formation of an inclusion complex and a non-inclusion complex. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 46-61 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin. “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the

addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

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, 25-31 and 46-61 are rejected on the ground of nonstatutory double patenting over claims 1-28 of U. S. Patent No. 7,888,328 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: claims 1-28 of U. S. Patent No. 7,888,328 recite a narrower genus of cladribine-cyclodextrin complex and composition comprising thereof wherein said cyclodextrin is hydroxypropyl-β-cyclodextrin and the weight ratio of from about 1:10 to about 1:16. Claims 12-28 of U. S. Patent No. 7,888,328 recite a product-by-process encompassed within the product-by-process of instant claims 46-61. Therefore claims 1-28 of U. S. Patent No. 7,888,328 supports a anticipation-type nonstatutory double patenting rejection over instant claims 1-8, 25-31 and 46-61.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is (571)270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1623

/Jonathan S Lau/
Examiner, Art Unit 1623

Notice of References Cited	Application/Control No. 12/986,310	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	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	WO 9718839 A1	05-1997	World Intellect	BAERT et al.	A61K 47/48
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*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
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012	02/15/2013							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
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	7	÷	✓							
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	35	÷	N							
	36	÷	N							

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CLAIM		DATE								
Final	Original	10/18/2012	02/15/2013							
	37	÷	N							
	38	÷	N							
	39	÷	N							
	40	÷	N							
	41	÷	N							
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	64	÷	N							

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12986310
Filing Date	2011-01-07
First Named Inventor	Nicholas S. BODOR
Art Unit	1623
Examiner Name	Jonathan S. LAU
Attorney Docket Number	20009904-0067

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/J.L./	1	99/62958	WO	A1	1999-12-09	Janssen Pharmaceutica N.V.	Corresponds to JP 2002-517521	☐
/J.L./	2	98/55148	WO	A1	1998-12-10	Janssen Pharmaceutica N.V.	Corresponds to JP 2002-511073	☐

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/Jonathan Lau/ 02/15/2013

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	Application Number	12986310
	Filing Date	2011-01-07
	First Named Inventor	Nicholas S. BODOR
	Art Unit	1623
	Examiner Name	Jonathan S. LAU
	Attorney Docket Number	20009904-0067

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/J.L./	1	Drugs in Japan (Nihon Iyakuhinn Shu), 2004 edition, JIHOU Inc. March 1, 2003, pp. 651-654, "Cladrivine" (especially, "Composition") - relevance explained in January 10, 2012, Japanese Official Action	☐
/J.L./	2	Official Action issued on January 10, 2012, in corresponding Japanese Patent Application No. 2006-509371, and an English language translation of the Official Action.	☒

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EXAMINER SIGNATURE

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	Application Number	12986310
	Filing Date	2011-01-07
	First Named Inventor	Nicholas S. BODOR
	Art Unit	1623
	Examiner Name	Jonathan S. LAU
	Attorney Docket Number	20009904-0067

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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☐ See attached certification statement.

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Signature	/Mary Katherine Baumeister/	Date (YYYY-MM-DD)	2012-08-09
Name/Print	Mary Katherine Baumeister	Registration Number	26,254

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EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1	"7888328".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:12
S2	127	((NICHOLAS) near2 (BODOR)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:12
S3	3	((YOGESH) near2 (DANDIKER)).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:12
S4	127	S2 or S3	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:12
S5	5	S4 and cladribine	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:13
S6	430	amorphous near9 cyclodextrin	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:41
S7	168	S6 and @ad<="20040204"	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:45
S8	9	S7 and (cladribine or adenosine)	US-PGPUB; USPAT; USOCR	ADJ	ON	2013/02/15 09:45

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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
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(74) Agent: DE CORTE, Filip; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: SOLID MIXTURES OF CYCLODEXTRINS PREPARED VIA MELT-EXTRUSION

(57) Abstract

Process for preparing a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient characterized in that said process comprises a melt-extrusion step, wherein the active ingredient is embedded into the cyclodextrin carrier.

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SOLID MIXTURES OF CYCLODEXTRINS PREPARED VIA MELT-EXTRUSION

The present invention involves a process for preparing solid mixtures by melt-extrusion comprising one or more active ingredients, preferably one or more practically insoluble active ingredients and one or more cyclodextrins. The invention further concerns pharmaceutical compositions comprising the above mixture.

WO 94/11031, published on May 5, 1994, discloses a method of manufacturing a high-quality enclosure compound using extrusion techniques. In this document the extrusion of cyclodextrins together with an active ingredient is mentioned. However, the document discloses the use of a wet mixture (i.e. including water or another solvent) to feed into the extruder.

French patent application 2,705,677 published on December 2, 1994 describes micro-granules obtained by extrusion-spheronisation containing a cyclodextrin. The extrusion-spheronisation technique is the combination of an agglomeration technique, i.e. extrusion, and a shaping technique, i.e. the spheronisation. Said patent application actually teaches the formation of microgranulates containing β-cyclodextrin (Kleptose®) and microcrystalline cellulose (Avicel®) and as active ingredients ketoprofen and paracetamol. The extrusion technique used in the above-mentioned patent application consists in preforming a humid mass by forcing said human mass through a nozzle thus forming long strands of extruded material. The document does not mention melt-extrusion at all.

EP 0,665,009, published as international application on April 24, 1994, discloses a method of dislocating the crystalline condition of crystalline medicine by extruding said crystalline material as such, i.e. without any excipient such as cyclodextrins.

In J. Pharm. Pharmacolog., vol 44, No 2, pages 73-8, Uekama *et al* show how amorphous nifedipine powders were prepared by spray-drying with hydroxypropyl-β-cyclodextrins. The document does not mention melt-extrusion.

In Pharm. Weekbl. Sci. Ed., 1988, vol 10, No 2, page(s) 80-85, Van Doorne *et al* , the complex formation between β-cyclodextrins and six antimicotic imidazole derivatives was studied. In said study gels and creams comprising antimicotics were prepared

whereby a 1.8 % solution of β-cyclodextrin was added instead of purified water. There is no mentioning of extrusion at all.

In J. Antimicrob. Chemother., 1993, vol 32, No 3, pages 459-463, Hostetler *et al* describe the effect of hydroxypropyl-β-cyclodextrin on the efficacy of oral itraconazole in disseminated murine cryptococcosis. In said document the authors describe how itraconazole is solubilized in hydroxypropyl-β-cyclodextrin resulting in a 100 ml solution. There is no mentioning at all of an extrusion process.

In Jpn. J. Med. Mycol., 1994, vol 35, No 3, page 263-267, Mikami *et al* describe the effect of carrier solvents on the efficacy of oral itraconazole therapy in aspergilossis in mice. Again this document discloses itraconazole being solubilized in hydroxypropyl-β-cyclodextrin. There is no mentioning of extrusion techniques.

In "Effect of 2-Hydroxypropyl-β-cyclodextrin on Crystallization and Polymorphic Transition of Nifedipine in Solid State", Pharmaceutical research, vol 11, No 12, 1994, Uekama et al. describe a glassy mixture of 2-hydroxypropyl-β-cyclodextrin obtained by heating said mixture and immediately cooling said mixture to 0 degrees Celsius. There is no teaching that this mixture can be extruded.

US 5,009,900 describe glassy matrices that are useful for introducing and/or retaining and/or stabilizing the volatile and/or labile components in cooked and uncooked food products. These glassy matrices comprise chemically modified starch having a dextrose equivalent not greater than about 2; maltodextrin, corn syrup solids or a polydextrose, and a mono- or disaccharide. The document does disclose extrusion to form glassy matrices. However, there is no specific mentioning of cyclodextrins and of therapeutically or pharmaceutically active ingredients.

None of the above mentioned documents disclose the present invention.

Although WO 94/11031 and French patent application 2,705,677 disclose extrusion of mixtures of cyclodextrins and actives ingredients, said documents do not mention the use of meltextrusion. The technique described in WO 94/11031 and French patent application 2,705,677 has a main disadvantage, that a humid mass needs to be prepared which requires adding to the cyclodextrin and the active ingredient a certain amount of water and in most cases others solvents such as ethanol or methanol. Removing the water and/or other solvents is often a troublesome production step, which often leads to

irreproducibility because not all of the solvent can be removed. Moreover, with practically insoluble active ingredients the amounts of water and/or adjuvant solvents needed make the above technique unpractical on a production scale. Another disadvantage of the technique described in the prior art is that the drying step can induce unwanted crystallization of the active ingredient.

These problems are solved in the present invention by the use of a melt-extrusion process to form solid mixtures comprising one or more cyclodextrins and insoluble active ingredients.

The present process is advantageously applicable when said active ingredient is sensitive to a solvent such as water or an organic solvent, because it does not require any solvent. The term "sensitive" used herein means that the active ingredient is readily (e.g. within about one hour) influenced by a solvent to such an extent that its physical, chemical and/or biological properties are substantially modified or changed.

The present process is further advantageous because it does not require a drying step, during which insoluble active ingredients often tend to crystallize.

The term "insoluble" hereinabove and hereinunder refers to three categories of compounds, i.e. the "very slightly soluble", "practically insoluble" and "insoluble".

The terms "very slightly soluble", "practically insoluble" or "insoluble" are to be understood as defined in the United States Pharmacopeia 23, NF 18 (1995) page 7, i.e. a "very slightly soluble" compound requires from 1000 to 10,000 parts of solvent for 1 part of solute; a "practically insoluble" or "insoluble" compound requires more than 10,000 parts of solvent for 1 part of solute. The solute referred to in these cases are water or aqueous solutions.

Three examples of this type of insoluble compounds are : itraconazole, loviride and (±)-ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate (hereinafter referred to as compound 1).

Itraconazole is an art-known antifungal. Loviride is an art-known anti-retrovirally active compound, particularly useful in treating HIV-infected patients.

(±)-Ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate is described as compound No. 3, in WO 95/27704 published on October 19, 1995.

The compounds that are suitable to be used in this technique are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said one or more active ingredients with the cyclodextrin or cyclodextrins.

The term "active ingredient" further refers to compounds or mixtures of compounds which are pharmaceutically or therapeutically or cosmeticallly active for treating humans or animals.

The present invention provides a process for preparing a solid mixture comprising one or more cyclodextrins and an (insoluble) active ingredient, comprising a melt-extrusion step wherein one or more cyclodextrins are combined with the one or more active ingredients.

Melt-extrusion is a polymer extrusion technique which involves embedding an active ingredient in one or more carriers. In this technique the active ingredient and excipients are molten in the extruder and hence embedded in thermoplastic and thermomelting polymers. The resulting molten mass is then forced through one or more nozzles resulting in a thermoplastic strand or strands.

An extruder comprises an inlet structure, a cylindrical structure called "barrel", a die and a screw or screws. A schematic overview is shown in Figure 1.

The inlet structure mostly is funnel shaped.

The barrel may comprise one or more barrel units and the screw or screws extend through them.

Extruders are available in two general types, namely a single-screw extruder comprising one screw and a multi-screw extruder comprising two or more screws. While this invention can be carried out using either type of extruder, the use of a multi-screw extruder, particularly a twin-screw extruder is preferred. A twin-screw extruder (and a multi-screw extruder) is more efficient in that the plural screws interferring with

each other precludes follow-up movement of the active ingredient and, moreover, the intermeshing of the screws provides a high energy output physically.

An interesting mode of operating the screws is to operate them in a corotating mode.

The screw or screws may have different shapes such as, for example, a trapezoidal screw, a trapezoidal cut screw, trapezoidal reverse cut screw, ball screw, kneading paddle and these may be used in the desired combination.

The load fed into the extruder via the inlet structure is forced by the screw or screws to advance, shorn and blended by the screw within the barrel and extruded from the orifice or orifices of the die. The temperature of the barrel or of the barrel units can be controlled via a heating element or even if necessary by a cooling element.

The rotational speed of the screw can be set within the allowable range of the extruder used.

A person skilled in the art is able to select the screw geometry and combination of unit screws. The principal function of the screw is to transport, crush and knead the material that is being extruded.

The orifice configuration may be circular, elliptical, rectangular or hexagonal.

Hence, said melt-extrusion step comprises the following substeps :

a) mixing one or more cyclodextrins with the active ingredient or active ingredients,
b) optionally mixing additives,
c) heating the thus obtained mixture until melting of one of the components,
d) forcing the thus obtained mixture through one or more nozzles;
e) cooling the mixture till it solidifies.

If desired, as mentioned above, the thermomelting mixture comprising one or more cyclodextrins and active ingredient(s) may comprise any suitable additive. When, for instance, the cyclodextrin(s) or the active ingredient(s) or one of the other possible additives is apt to be oxidized, an anti-oxidizing agent may be incorporated, preferably in small amounts, such as, for instance 100 to 5000 ppm when compared to the total weight of the mixture. Furthermore, conventional auxiliary additives such as pigments, flavors, stabilizers, preservatives and buffers may be added.

If necessary conventional pharmacologically acceptable plasticizers, such as long chain alcohols, ethylene glycol, propylene glycol, thriethylene glycol, butanediols, pentanols, hexanols, polyethylene glycols, aromatic carboxylates (e.g. dialkyl phthalates, trimellitates, benzoates or terephthalates), aliphatic dicarboxylates or fatty acid esters can also be added. Preferably however, a plasticizer is not needed.

The term "melting" should be broadly interpreted. "Melting" can also refer to the fact that some transition is made to a glassy state, in which it is possible for one component of the mixture to get embedded into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming solid solutions, which show advantageous dissolution properties.

The possible formation of these solid solutions is one of the further advantages of the present invention. It will be appreciated by a person skilled in the art that mixing two or more solids, i.e. one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

A characteristic of the melt extruded mixtures of the present invention is the fact that they contain substantially less water or any other solvent than mixtures being extruded in an other way.

Preferably the present melt extruded mixtures contain no water or solvent, apart from the water or solvent that eventually is contained in the crystal structure of the active ingredient.

It will be appreciated that the temperature inside the extruder is an important parameter. When different barrel units are present, different temperatures can be applied. A person skilled in the art is able to establish the required temperatures by taking the desired type of cyclodextrin or cyclodextrins or even the complete mixture that is going to be extruded and observing the behaviour as a function of temperature with the aid of a melting point measuring instrument, such as a Kofler hot bench, a microscope hot stage type or a differential scanning calorimeter, e.g. type DSC 7 Series - Perkin Elmer.

The cooling can be performed without using any auxiliary means, i.e. it most often suffices to let the thermoplastic strand coming out of the extruder cool down to the ambient temperature of the production site. Of course, cooling aids may be used.

Once these thermoplastic strands are cooled down these strands can be milled to obtain a powdered form of the mixture of cyclodextrin or cyclodextrins and the active ingredient.

A person skilled in the art will appreciate that the milling can influence the physical characteristics of the extrudate. During milling the temperature of the material can rise because of the friction and also high shear forces are exerted on the material that is to be milled. Both temperature and mechanical or shear forces can result in a transition of the physical state of the material that is to be milled. A person skilled in the art has sufficient means at his disposal to control temperature and shear forces and thus to control the milling process.

The two processes, i.e. melt extrusion and milling can be combined into one configuration as is shown in Figure 1. The mixture of one or more cyclodextrins and one or more active ingredients in combination with possible other additives is feed via a funnel like inlet. The mixture is then melt-extruded and the mixture is forced through a nozzle onto a conveyor belt. While being transported on the conveyor belt the extrudate cools down. The cooled melt extrudate is fed into a chopper which forms pellets. These pellets may be further milled if required.

This powdered material still has the beneficial properties (high bioavailability, dissolution rate, etc.) and it can be used in the conventional way to prepare pharmaceutical, therapeutical or cosmetical solid dosage forms.

An additional advantage of the present invention is that the active ingredient as well as the cyclodextrins may be transformed in a amorphous form or even that a solid solution is formed. A person skilled in the art will appreciate that this modification of physical state from crystalline to amorphous or to solid solutions is highly advantageous for the dissolution.

The fact whether the melt extruded mixture contains amorphous material or contains a solid solution or consists essentially of amorphous material or a solid solution can be measured or checked using differential scanning calorimetry. When there is crystalline

material present in the melt extruded mixture a differential scanning calorimeter will show an endothermic melting peak. When amorphous material or a solid solution is mainly present in the melt extruded mixture a differential scanning calorimeter will not show an endothermic melting peak. Visual inspection of the melt extrudate allows for a distinction between amorphous material and a solid solution. In case the melt extrudate is opaque then both the cyclodextrin(s) and the active ingredient are in a amorphous form. In case melt extrudate is clear then a solid solution was formed.

Curves of differential scanning calorimetry are shown in Figures 2 to 7.

Interesting embodiments of the present invention are these melt extruded mixtures which consist mainly of amorphous material.

More interesting embodiments of the present invention are these melt extruded mixtures which consist essentially of amorphous material.

Even more interesting embodiments of the present invention are those melt extruded mixtures which consist mainly of a solid solution of the active ingredient or active ingredients in the cyclodextrin or the cyclodextrins.

Preferred embodiments of the present invention are those melt extruded mixtures which consist essentially of a solid solution of the active ingredient or active ingredients in the cyclodextrin or the cyclodextrins.

Another advantage of the present invention is that the granulation step in forming pharmaceutical, therapeutical or cosmetical compositions can be omitted, because the powdered material can simply be mixed with other excipients and compressed into, for instance, tablets or another solid pharmaceutical, therapeutical or cosmetical form.

Depending upon the characteristics of the melt extruded mixture, the size of the pellets of said melt extruded mixture or the mesh of the powder of said melt extruded mixture and, of course, dependent upon the other auxiliaries that are added to the unit dosage forms the unit dosage form may give immediate release or sustained release.

If desired, said solid pharmaceutical form may also be provided with a conventional coating to improve the appearance and/or the flavor (coated tablets) or additionally to target the release of the active ingredient.

Suitable tablets may have the following compositions and may be prepared in a conventional way. The amounts given are of course dependent upon the dose required for the pharmaceutical, therapeutic or cosmetic activity.

Composition A

milled melt extrudate	100 - 500 mg
microcrystalline cellulose	100 - 300 mg
crospovidone	10 - 200 mg
colloidal silicon dioxide	1 - 5 mg
sterotex	2 - 10 mg

Composition B

milled melt extrudate	100 - 500 mg
Microcelac (TM) (1)	200 - 300 mg
crospovidone	70 - 200 mg
talc	20 - 50 mg
sterotex	7 - 10 mg
colloidal silicon dioxide	1 - 5 mg
magnesium stearate	2 - 10 mg

The cyclodextrin to be used in the aforementioned compositions include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used in the invention include polyethers described in U.S. Patent 3,459,731. In general, unsubstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst.
Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can react with yet another molecule of alkylene oxide, the average molar substitution (MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit.

Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonylC_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

In the foregoing definitions the term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

Such ethers can be prepared by reacting the starting cyclodextrin with an appropriate O-alkylating agent or a mixture of such agents in a concentration being selected so that the desired cyclodextrin ether is obtained. The said reaction is preferably conducted in a suitable solvent in the presence of an appropriate base. With such ethers, the degree of substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more in particular 0.3 to 1 and the MS is in the range of 0.125 to 10, in particular of 0.3 to 3 and more in particular 0.3 to 1.5.

Of particular utility in the invention are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

A more novel type of substituted cyclodextrins is sulfobutylcyclodextrines. These type are also envisaged in the present invention.

The ratio of active ingredient over cyclodextrin may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of active ingredient over cyclodextrin range from about 1/10 to 10/1. More interesting ratios of active ingredient over cyclodextrin range from about 1/5 to 5/1. Most interesting ratios range from about 1/3 to 3/1. Preferred ratio is aabout 1/1.

The use of a mixture of cyclodextrins, either different types (α, β, γ) or different substitution (2-hydropropyl or methyl) or different substitution grades in sometimes recommendable to decrease the melting point.

Description of the drawings

Figure 1 is a schematic representation of a configuration for carrying out the present invention.

Figure 2 is a differential scanning calorimetry curve (DSC curve) of non-milled Batch No 1 material. (see Example 1)

Figure 3 is a differential scanning calorimetry curve of milled Batch No 1 material (see Example 1)

Figure 4 is a differential scanning calorimetry curve of Batch No 2 material (see Example 1)

Figure 5 is a differential scanning calorimetry curve of of Batch No 3 material (see Example 1)

Figure 6 is a differential scanning calorimetry curve of of Batch No 4 material (see Example 1)

Figure 7 is a differential scanning calorimetry curve of of Batch No 5 material (see Example 1)

Example 1

Extruded samples of active ingredient with hydroxypropyl-β-cyclodextrin (HP-β–CD) were obtained using a Twin Screw Extruder type MP19 APV Baker (commercially available from the company APV Baker) with a die having a orifice of 3 mm. The process parameters for each individual experiment are shown in the table 1. This type of extruder has a L/D ratio of 15 and a screw pattern : 4D FS - 4x30 FP - 4x60 FP - 4x90 P - 4x60 RP - 2.5D FS - 2x30 FP - 2x60 FP - 2x90 P - 3x60 RP - 3 DFS. (4D refers to a transportelement having a length of 4 times the screw diameter of the feed screw type; 4x30 FP refers to 4 forward paddles positioned with mutual angle of 30

degrees, 4x60 RP refers to a working zone having reverse paddles positioned with a mutual angle of 60 degrees)

In this type of extruder the mixture is fed by a feeding screw turning a constant feeding speed (v1) (A feeding speed of 10 revolutions per minute amounts to a feeding speed of 1,5 kg per hour) onto the twin transporter screws having a diameter of 18 mm turning at a transporter speed (v2). These speeds are rotational speeds (revolutions per minute).

The mixture is then transported into a first heating zone (t1). Here the rate of transport diminished by a difference of the configuration of the twin transporter screws i.e. the rotational transporter speed v2 remains the same but the material does not progress as quickly.

Subsequently, the molten mass is transported by again normal configuration twin transporter screws to a second heating zone (t2) where the rate of transport is again diminished by a difference of configuration of the twin transporter screws.

After this second heating the thermomelting mixture is transported to the nozzle of the apparatus.

Table 1

mixture	Batch. No	t_1 (°C)	t_2 (°C)	t_p (°C)	v1 (rpm)*	v2 (rpm)*
compound 1 / HP-β-CD : 1/3	1	256	283	280	10	100
itraconazole / HP-β-CD : 1/1	2	263	265	279	10	20
itraconazole / HP-β-CD : 1/3	3	264	265	280	10	20
loviride / HP-β-CD : 1/1	4	274	285	292	10	80
loviride / HP-β-CD : 1/3	5	258	265	274	10	20

* rpm = revolutions per minute

- t_1 : temperature of the first heating zone
- t_2 : temperature of the second heating zone

- t_p : temperature inside the barrel
- v_1 : rate of feeding screw
- v_2 : twin transporter screws speed(rotational).

In every case the mixture of active ingredient and 2-hydroxypropyl-β–CD gave a solid solution.

Example 2

Extruded samples of active ingredient with dimethyl-β-cyclodextrin (DM-β–CD) were obtained using extruder type MP19 - APV Baker with the process parameters as shown in the table 2.

Table 2

mixture	Batch. No.	t_1 (°C)	t_2 (°C)	t_p (°C)	v_1 (1) (rpm)*	v_2 (rpm)*
compound 1 / DM-β-CD : 1/1	6	241	245	254	0	20
itraconazole / DM-β-CD : 1/1	7	239	240	253	0	20
loviride / DM-β-CD : 1/1	8	248	250	263	0	20

* rpm = revolutions per minute
(1) The apparatus was fed manually, without using the feeding screw.
In every case the mixture of active ingredient and DM-β-CD.

- t_1 : temperature of the first heating zone
- t_2 : temperature of the second heating zone
- t_p : temperature inside the barrel
- v_1 : feeding screw speed (rotational)
- v_2 : twin transporter screw speed (rotational).

Example 3

The dissolution of the melt extrudate of Batch No 1 was compared with the dissolution of the "physical mixture" (i.e. the mixture of the two component in the ratio as shown for Batch No. 1, but not melt extruded).

An amount of 100 mg of milled melt extrudate of Batch No 1 was added to a volume of 900 ml of artificial gastric juice at a temperature of 37 degrees Celsius. The stirring method used was the peddle method with a peddle moving at 100 rotations per minute. Using UV spectrometry the relative amount of dissolved extrudate was measured during 1 hour.

The same procedure for the "physical mixture" was followed.

The results of this dissolution process are shown in Table 3

Table 3

time mixture (minutes)	milled extrudate Batch No 1 (% of total amount dissolved)	corresponding physical (% of total amount dissolved)
0	0.00	0.00
5	62.10	1.71
15	70.20	14.67
30	72.63	21.06
45	74.07	26.10
60	74.25	28.35

Example 4

The melting behaviour was measured by using differential scanning calorimetry. The calorimeter used is the Perkin-Elmer 7 Series Thermal Analysis System. In all cases the rate of heating was set at 20 degrees Celsius per minute.

Figure 2 shows the DSC curve of melt extrudate of Batch No 1 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was a clear solution , thus indicating that the non-milled melt extrudate of Batch No 1 is a solid solution.

Figure 3 shows the DSC curve of melt extrudate of Batch No 1 after milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was a clear solution , thus indicating that the milled melt extrudate of Batch No 1 is a solid solution.

Figure 4 shows the DSC curve of meltextrudate of Batch No 2 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was not a clear solution, thus indicating that the non-milled melt extrudate of Batch No 2 is a mixture of amorphous material.

Figure 5 shows the DSC curve of meltextrudate of Batch No 3 before milling. The curve shows a small endothermic peak. The data on said small peak are as follows : X1 = 117.600 degrees Celsius, X2 = 143.200 degrees Celsius, Peak at 132.695 degrees Celsius, Area is 38.126 mJ, ΔH is 3.768 J/g, Height is 1.520 mW and the onset is at 125.816 degrees Celsius. Said small peak is very probably due to an impurity in the cyclodextrins. It was established that the non-milled melt extrudate of Batch No 3 is a mixture of amorphous material.

Figure 6 shows the DSC curve of meltextrudate of Batch No 4 before milling. The curve shows a few small endothermic peaks. Hence, it was established that the non-milled melt extrudate of Batch No 4 is a mixture of amorphous material containing small amounts of crystalline material

Figure 7 shows the DSC curve of meltextrudate of Batch No 5 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was not a clear solution, thus indicating that the non-milled melt extrudate of Batch No 5 is a mixture of amorphous material.

Example 5

The melt extrudate of Batch No. 1 was milled and sieved. By mixing the appropriate amounts a tablet having the following composition was prepared in an art-known way :

milled extrudate batch No 1	480 mg
microcrystalline cellulose	218 mg
Aerosil	3 mg
magnesium stearate	5 mg
crospovidone	144 mg

Claims

1. Process for preparing a solid mixture comprising one or more cyclodextrins and one or more active ingredients characterized in that said process encompasses a melt-extrusion step, wherein the active ingredient is embedded into the cyclodextrin carrier.

2. A process as claimed in claim 1, wherein the melt-extrusion process comprises the following substeps :
   a) mixing one or more cyclodextrins with one or more active ingredients, and
   b) optionally mixing additives;
   c) heating the thus obtained mixture until melting of one of the components;
   d) forcing the thus obtained mixture through one or more nozzles;
   e) cooling the mixture till it solidifies.

3. A solid mixture obtainable by the process as described in any of claims 1 or 2, with the proviso that nifedipine in combination with 2-hydroxypropyl-β-cyclodextrin is excluded.

4. A solid mixture as claimed in claim 3 characterized in that the active ingredient or active ingredients are insoluble according to the definition of US Pharmacopeia.

5. A solid mixture as claimed in claims 3 or 4, wherein substantially only one type of cyclodextrin is present.

6. A solid mixture as claimed in any of claims 3 to 5 wherein a cyclodextrin is hydroxypropyl-β-cyclodextrin.

7. A solid mixture as claimed in any of claim 3 to 5 wherein a cyclodextrin is dimethyl-β-cyclodextrin.

8. A solid mixture as claimed in any of claims 3 to 7, wherein the active ingredient is itraconazole.

9. A solid mixture as claimed in any of claims 3 to 7 wherein the active ingredient is loviride.

10. A solid mixture as claimed in any of claims 3 to 7 wherein the active ingredient is (±)-ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate.

11. A pharmaceutical composition comprising milled melt extrudate and other excipients.

12. A process for preparing a pharmaceutical composition as claimed in claim 11 characterized by milling appropriately the solid mixture as claimed in any of claims 4 to 10, intimately mixing the thus obtained powdered material with other pharmaceutically acceptable excipients and further processing into pharmaceutical dosage forms.

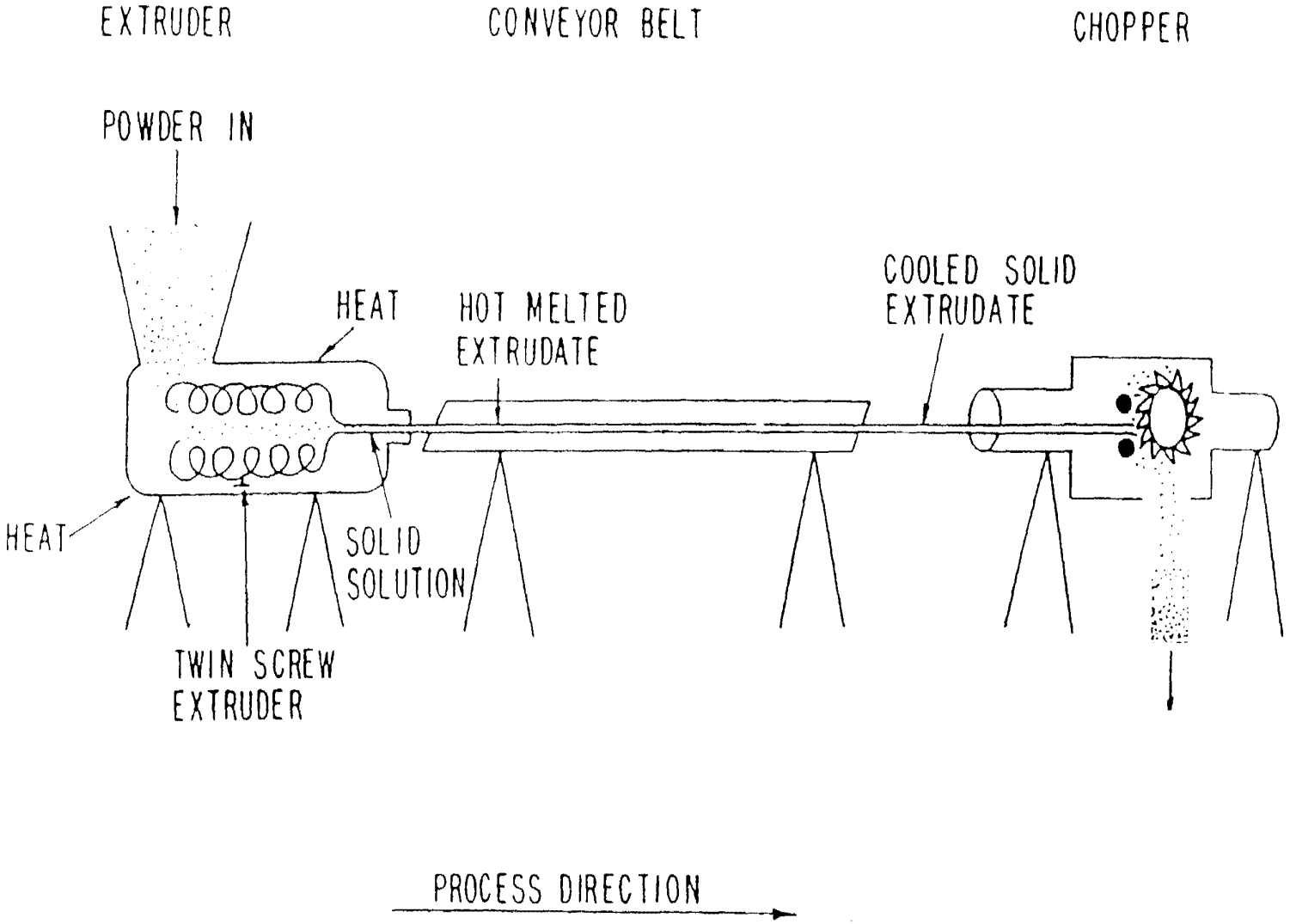

EXTRUDER
CONVEYOR BELT
CHOPPER
POWDER IN
HEAT
HOT MELTED EXTRUDATE
COOLED SOLID EXTRUDATE
HEAT
SOLID SOLUTION
TWIN SCREW EXTRUDER
PROCESS DIRECTION

Fig. 1

Fig. 2

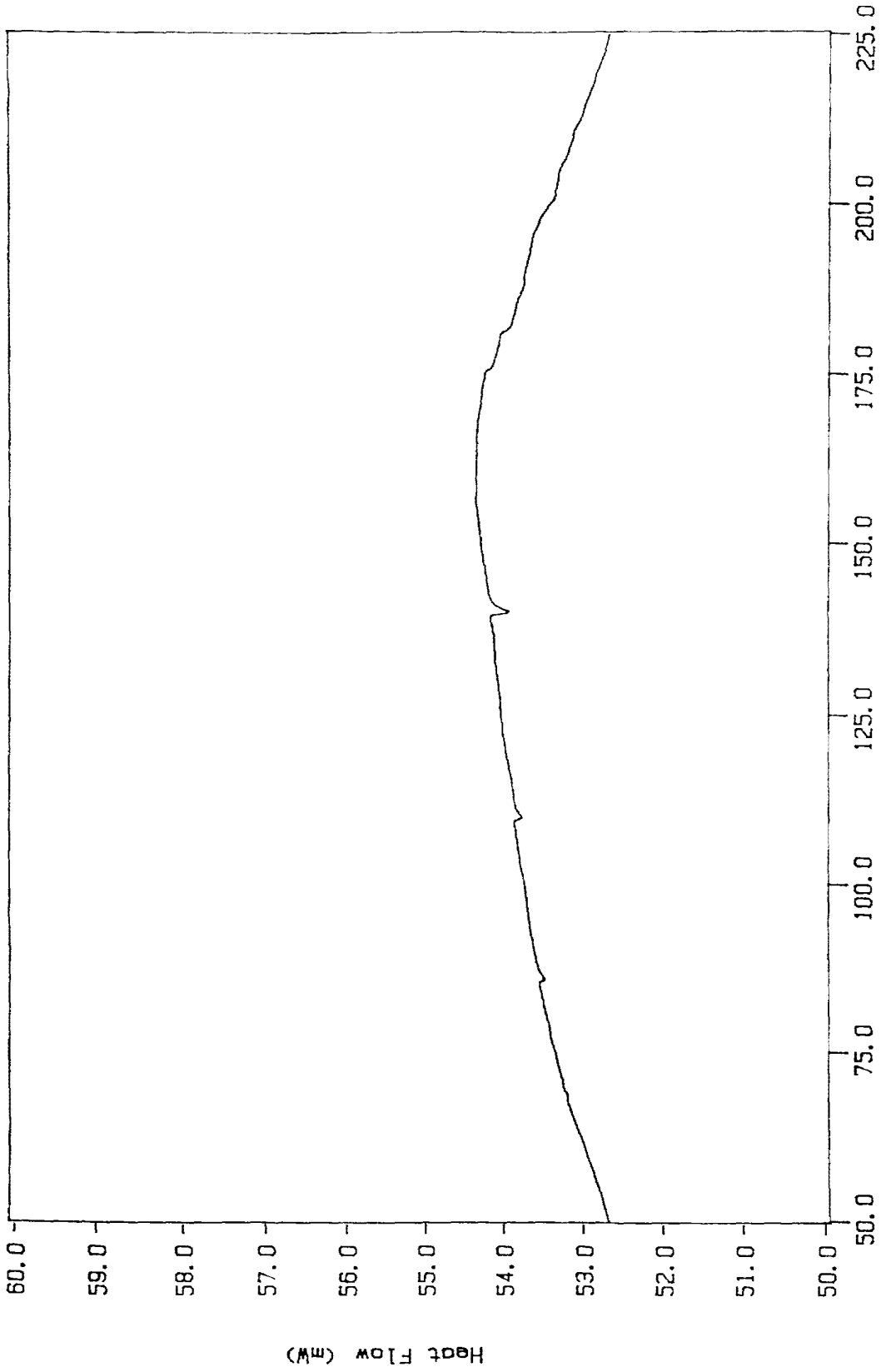

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
Temperature (°C)
240

Fig. 3

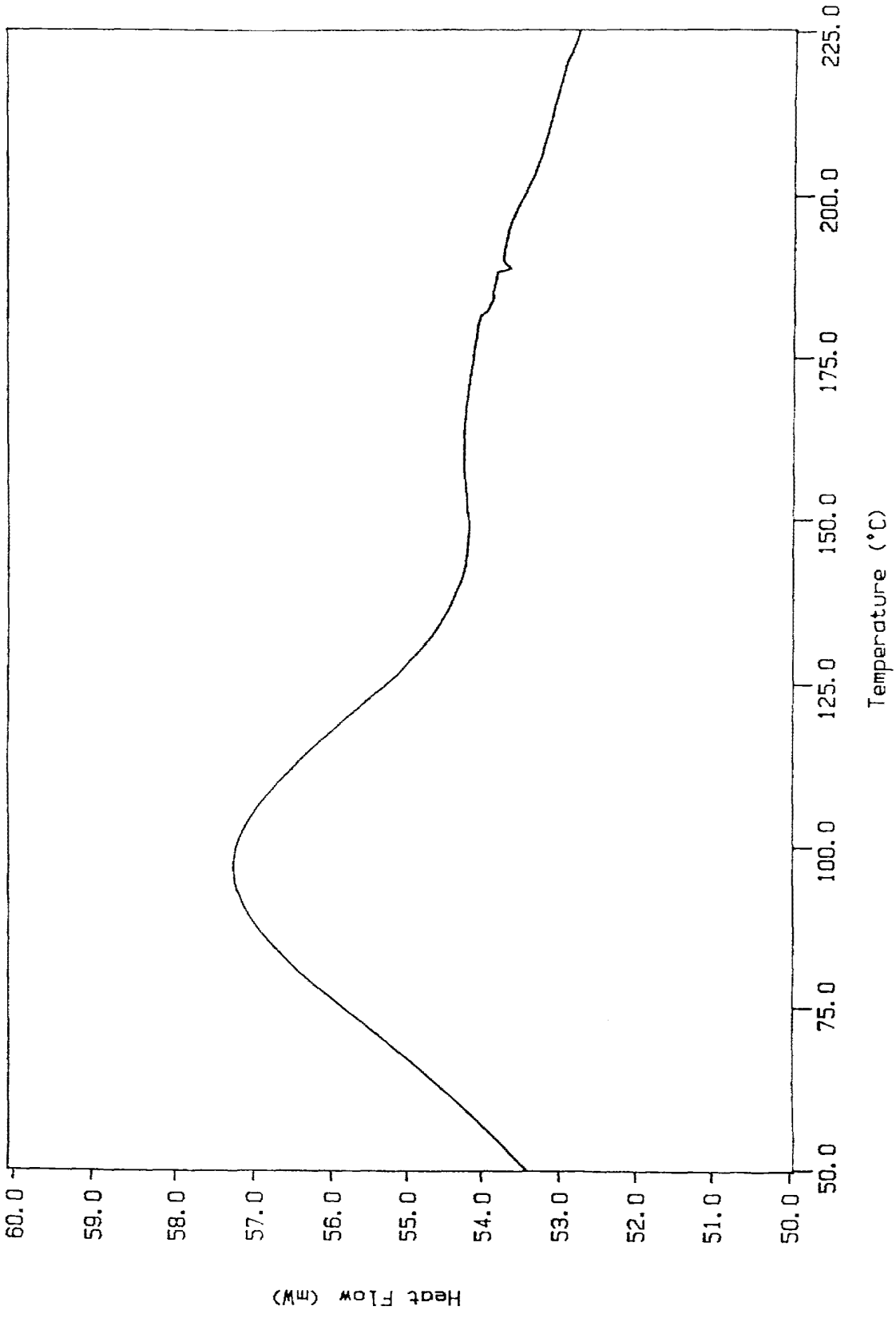

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
Temperature (°C)
241

Fig. 4

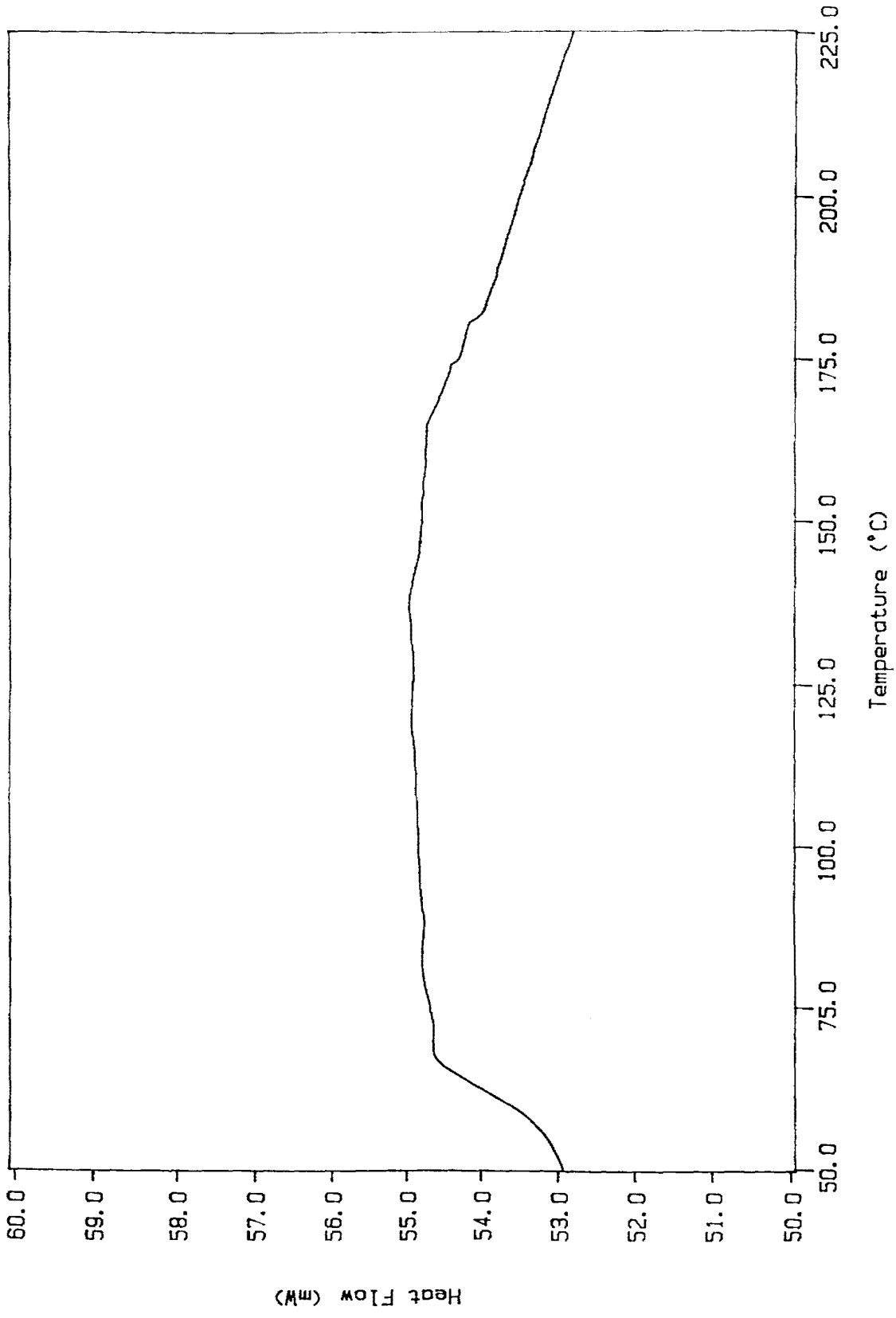

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
Temperature (°C)
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
242

Fig. 5

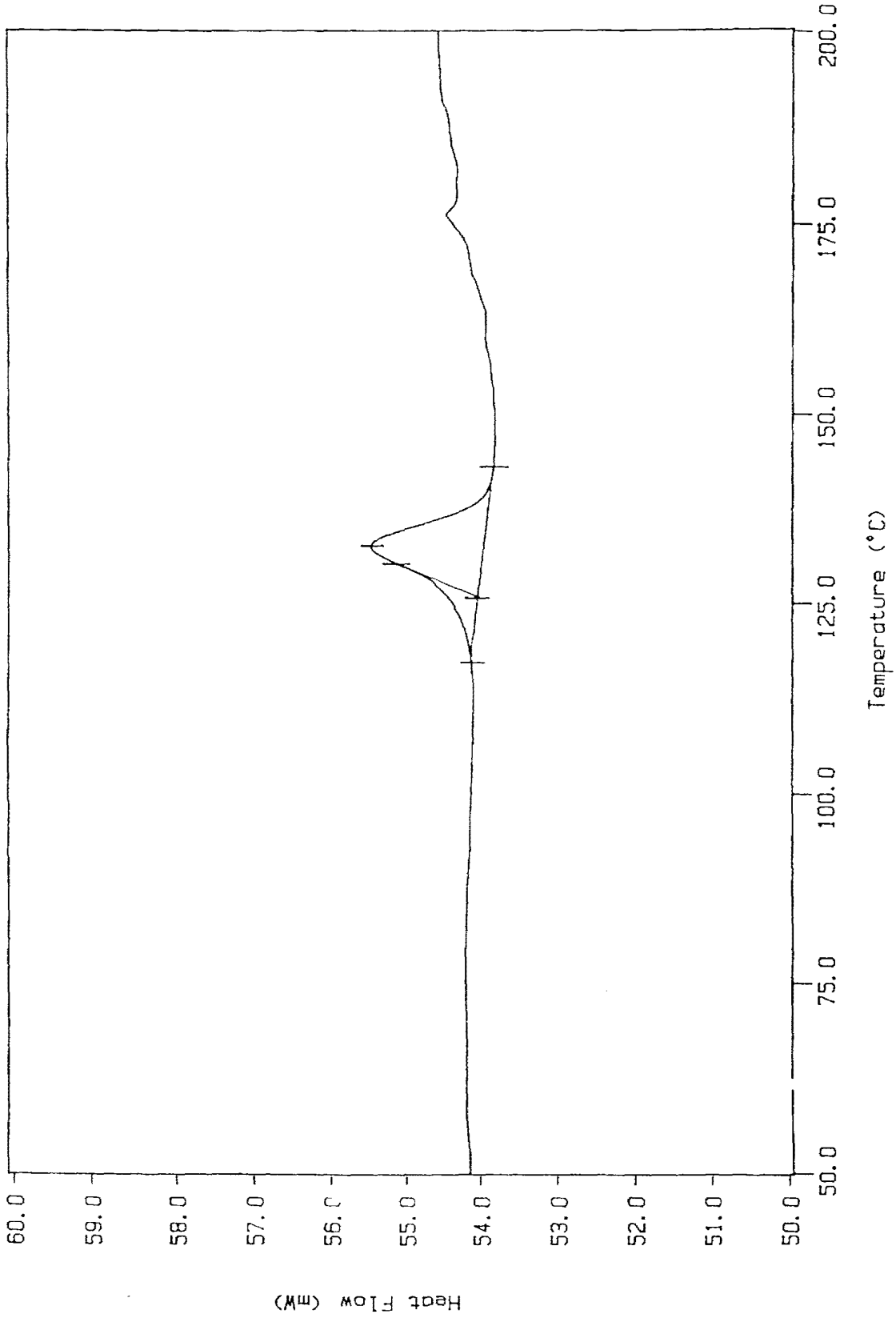

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
Temperature (°C)
243

Fig. 6

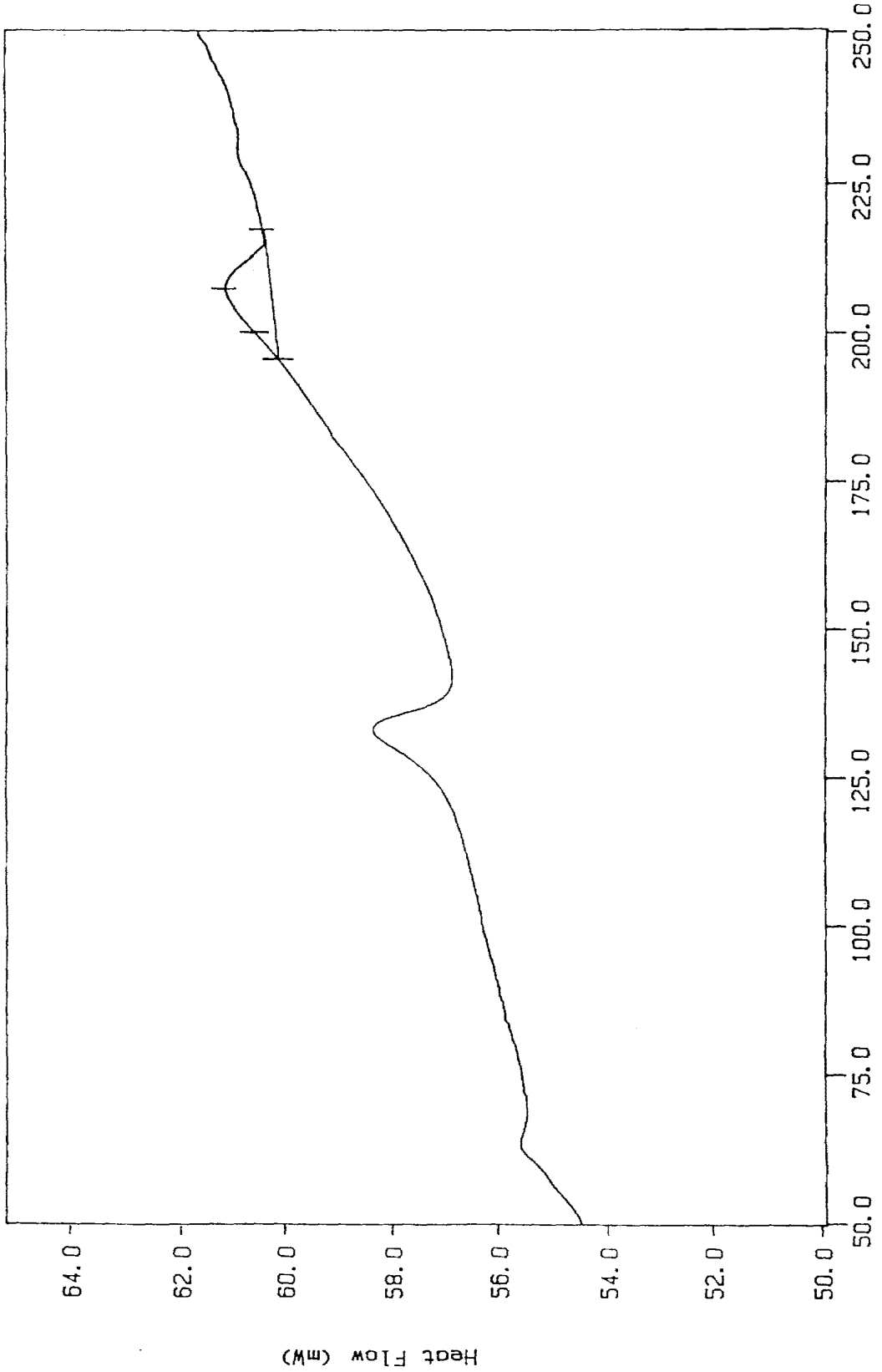
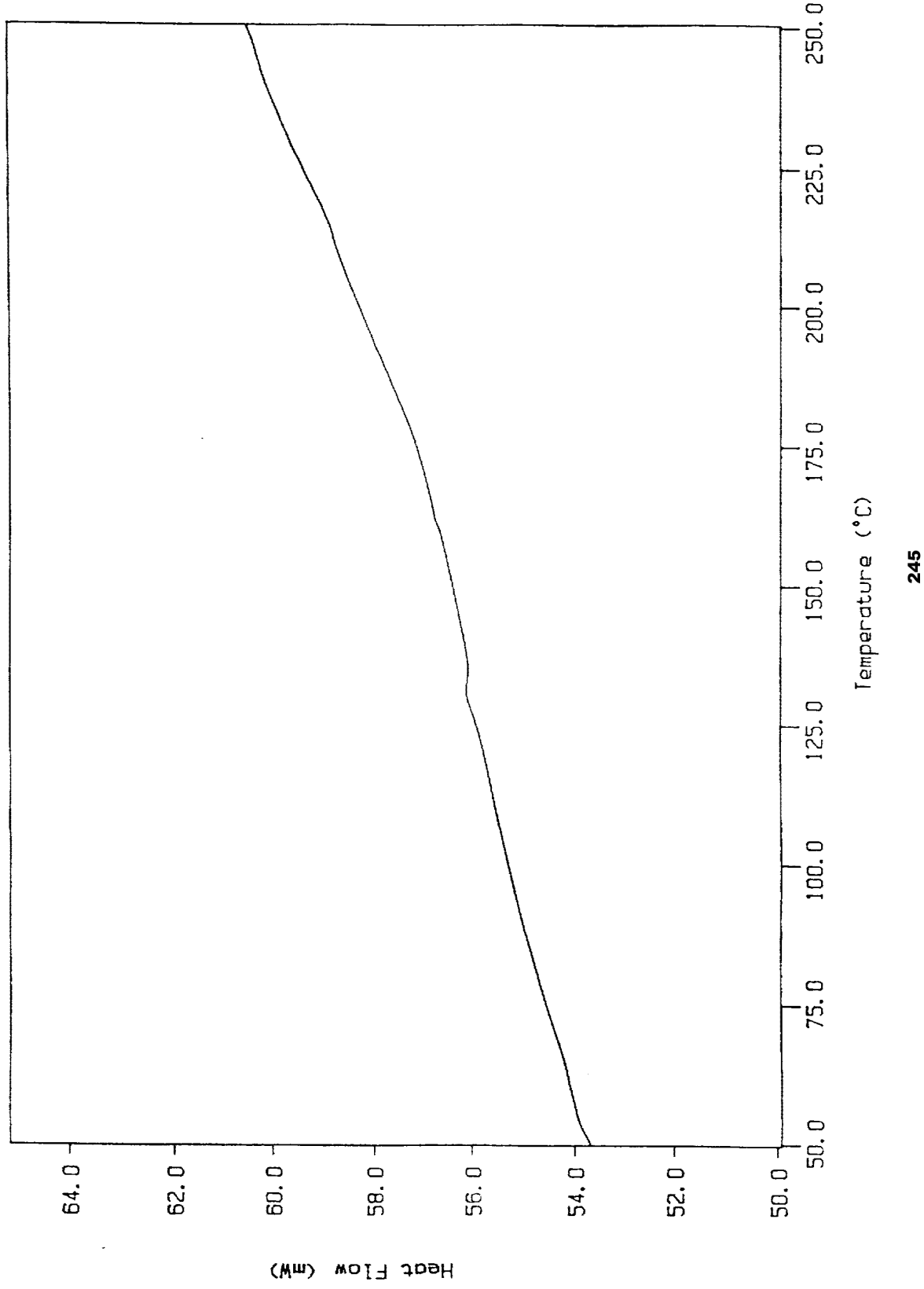

Heat Flow (mW)
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
250.0
Temperature (°C)
244

Fig. 7


Heat Flow (mW)
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
250.0
Temperature (°C)
245

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 96/05118

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 11031 A (NIPPON SHINYAKU CO LTD) 26 May 1994 cited in the application see abstract	1-12
Y	FR 2 705 677 A (ROQUETTE FRERES) 2 December 1994 cited in the application see abstract see examples see claims	1-12
X	EP 0 665 009 A (NIPPON SHINYAKU COMPANY, LIMITED.) 2 August 1995 cited in the application see abstract see examples see claims	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

2

Date of the actual completion of the international search
24 February 1997

Date of mailing of the international search report
17.03.97

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/05118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. PHARM. PHARMACOL., VOL. 44, NO. 2, PAGE(S) 73-8, 1992, XP002002172 UEKAMA, KANETO ET AL: "Inhibitory effect of 2- hydroxypropyl -.beta.- cyclodextrin on crystal growth of nifedipine during storage: superior dissolution and oral bioavailability compared with poly(vinylpyrrolidone) K-30" cited in the application * paragraph Materials and methods * see figures	1-12
Y	PHARM. WEEKBL. SCI. ED., 1988, VOL. 10, NO. 2, PAGE(S) 80-85, XP002002173 VAN DOORNE H. ET AL: "Formation and antimicrobial activity of complexes of beta- cyclodextrin and some antimycotic imidazole derivatives" cited in the application see abstract * paragraph Results and discussion * see page 85, left-hand column	1-12
Y	J. ANTIMICROB. CHEMOTHER., 1993, VOL. 32, NO. 3, PAGE(S) 459-463, XP002002174 HOSTETLER J.S. ET AL: "Effect of hydroxypropyl-beta-cyclodextrin on efficacy of oral itraconazole in disseminated murine cryptococcosis" cited in the application see abstract * paragraph Results *	1-12
Y	JPN. J. MED. MYCOL., 1994, VOL. 35, NO. 3, PAGE(S) 263-267, XP002002175 MIKAMI Y. ET AL: "Effect of carrier solvents on the efficacy of oral itraconazole therapy in aspergillosis in mice" cited in the application see abstract see figures	1-12
Y	PHARM. RES., VOL. 11, NO. 12, PAGE(S) 1766-70, 1994, XP002002176 HIRAYAMA, FUMITOSHI ET AL: "Effect of 2-hydroxypropyl -.beta.- cyclodextrin on crystallization and polymorphic transition of nifedipine in solid state" cited in the application see abstract * paragraph Results and discussion * -/--	1-12

2

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 96/05118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 009 900 A (LEVINE HARRY ET AL) 23 April 1991 cited in the application see examples see claims -----	1-12

2

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 96/05118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7,11-12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds, which are defined by the general definition of the active ingredient used in the claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

in the claims, and to the general idea underlying the application (see Guidelines, chapter III, paragraph 2.3).

Claims searched incompletely: 1-7,11-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 96/05118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411031 A	26-05-94	AU 5376994 A	08-06-94
FR 2705677 A	02-12-94	IT 1265964 B	16-12-96
EP 665009 A	02-08-95	AU 5160793 A	09-05-94
		WO 9408561 A	28-04-94
US 5009900 A	23-04-91	CA 2025647 A	03-04-91

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SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/986,310	01/07/2011	514	1623	20009904-0067

APPLICANTS

Nicholas S. Bodor, Bal Harbour, FL;
Yogesh Dandiker, Toronto, CANADA;

**** CONTINUING DATA ***************************

This application is a CON of 10/551,205 11/14/2006 PAT 7,888,328
which is a 371 of PCT/US2004/009387 03/26/2004
which claims benefit of 60/458,922 03/28/2003
and claims benefit of 60/484,756 07/02/2003
and claims benefit of 60/541,247 02/04/2004

**** FOREIGN APPLICATIONS ***************************

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01/18/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JONATHAN S LAU/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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UNITED STATES

TITLE

ORAL FORMULATIONS OF CLADRIBINE

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FIRST INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 4

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Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
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	US-6,239,118 B1	05-29-2001	Shatz et al.	
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/J.L./	US-6,699,849	03-02-2004	Loftsson et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	
/J.L./	EP 0 197 571 A2	10-15-1986	Janssen Pharmaceutica N.V.							X	
	WO 90/12035A1	10-18-1990	Janssen Pharmaceutica N.V.							X	
	DE 31 18 218 A1	04-22-1982	Chinoin Gyogyszer Es Vegyeszet						X	X	
	DE 33 17 064 A1	11-15-1984	Consortium Elektrochem Ind						X	X	
	GB 2 189 245 A	10-21-1987	American Maize-Products Company							X	
	EP 0 149 197 B1	07-24-1985	Janssen Pharmaceutica N.V.	X						X	
	EP 0 094 157 A1	11-16-1983	Janssen Pharmaceutica N.V.							X	
/J.L./	WO 99/42111	08-26-1999	Cyclops, ehf								

Examiner Signature	/Jonathan Lau/	Date Considered	02/15/2013

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Attorney Docket No.	0056192-000067

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/J.L./	TARASIUK et al., "Stability of 2-Chloro-2'-Deoxyadenosine at Various pH and Temperature", *Archivum Immunologiae et Therapiae Experimentalis*, Vol. 42, pp. 13-15, 1994, published by Birkhauser Publishers Ltd., Basel, Switzerland
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Attorney Docket No.	0056192-000067

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/J.L./	BAKTHIAR et al., "A study of the complexation between dimethyl-β-cyclodextrin and steroid hormones using electrospray ionization mass spectrometry", *Rapid Communications in Mass Spectrometry*, Vol. 11, pp. 1478-1481, 1997, John Wiley And Sons Ltd, England
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Examiner Signature	/Jonathan Lau/	Date Considered	02/15/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 4 of 4

Complete if Known

Application Number	
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

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	OTHER
/J.L./	International Search Report dated October 12, 2004 for PCT/US2004/009387, filed March 26, 2004
/J.L./	PCT International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2004/009387, International Filing date March 26, 2004.

Examiner Signature	/Jonathan Lau/	Date Considered	02/15/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor, Yogesh Dandiker)	2/15/2013	JSL
EAST - see attached notes	2/15/2013	JSL
Google Scholar - see attached notes	2/15/2013	JSL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nicholas S. BODOR et al.	)	**MAIL STOP AMENDMENT**
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
Filed: January 7, 2011	)	Group Art Unit: 1623
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100

REPLY AND AMENDMENT

In response to the Office Action dated February 25, 2013, please first amend the above-identified patent application as follows:

AMENDMENTS TO THE SPECIFICATION:

Please replace the first paragraph and its heading on page 1 with the following:

CROSS-REFERENCE TO EARLIER APPLICATIONS

This application is a continuation of prior copending US Application No. 10/551,205 filed November 14, 2006, now ~~allowed~~U.S. Patent No. 7,888,328, which is the US national stage of International Application No. PCT/US2004/009387, filed March 26, 2004, which claims benefit under 35 U.S.C. § 119(e) of United States Provisional Application No. 60/458,922, filed March 28, 2003; of United States Provisional Application No. 60/484,756, filed July 2, 2003; and of United States Provisional Application No. 60/541,247, filed February 4, 2004, all of said applications being hereby incorporated by reference herein in their entireties and relied upon.

Electronic Patent Application Fee Transmittal

Application Number:	12986310
Filing Date:	07-Jan-2011
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Attorney Docket Number:	20009904-0067

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	12	80	960
Independent claims in excess of 3	1201	1	420	420
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1380**

Electronic Acknowledgement Receipt

EFS ID:	15887589
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	28-MAY-2013
Filing Date:	07-JAN-2011
Time Stamp:	18:44:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1380
RAM confirmation Number	8981
Deposit Account	193140
Authorized User	BAUMEISTER, MARY KATHERINE

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 **262** (Patent application and reexamination processing fees)

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 1.20 (Post Issuance 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		Amendment.PDF	1187619 1c400c71df815a15e645ffbd60fa36a6e5a9ac03	yes	58

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Specification	2	2
	Claims	3	14
	Applicant Arguments/Remarks Made in an Amendment	15	58

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	31842 6e5c34b2cb2eb9f9990e31b9c3495b2f2824ea7f	no	2

Warnings:

Information:

Total Files Size (in bytes):	1219461

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 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/986,310	Filing Date 01/07/2011	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/28/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 76	Minus	** 64	= 12	X $80 =	960
	Independent (37 CFR 1.16(h))	* 5	Minus	***4	= 1	X $420 =	420
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	1380

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

LIE
/LASHAWN MORGAN/

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.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Original) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. (Original) The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.

3. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

5. (Original) The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

6. (Original) The composition according to Claim 5, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

7. (Original) The composition according to Claim 1, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point

located on the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

8. (Original) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

9. (Withdrawn) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

10. (Withdrawn) The method according to Claim 9, wherein the complex is saturated with cladribine.

11. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

12. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

13. (Withdrawn) The method according to Claim 9, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

14. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

15. (Withdrawn) The method according to Claim 9, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

16. (Withdrawn) The method according to Claim 9, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

17. (Withdrawn) A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

18. (Withdrawn) The method according to Claim 17, wherein the complex is saturated with cladribine.

19. (Withdrawn) The method according to Claim 17, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

20. (Withdrawn) The method according to Claim 19, wherein the cladribine-responsive condition is multiple sclerosis.

21. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

22. (Withdrawn) The method according to Claim 17, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

23. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

24. (Withdrawn) The method according to Claim 17, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. (Original) A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

26. (Original) The complex according to Claim 25, saturated with cladribine.

27. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

28. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

29. (Original) The complex according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

30. (Original) The complex according to Claim 29, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

31. (Original) The complex according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

32. (Withdrawn) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 25, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

33. (Withdrawn) The process according to Claim 32, further comprising a filtration step following step (ii).

34. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

35. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

36. (Withdrawn) The process according to Claim 34, wherein step (i) is performed with stirring.

37. (Withdrawn) The process according to Claim 36, wherein step (i) is performed for a period of from about 6 to about 9 hours.

38. (Withdrawn) The process according to Claim 32, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

39. (Withdrawn) The process according to Claim 32, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

40. (Withdrawn) The process according to Claim 39, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

41. (Withdrawn) The process according to Claim 34, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i), or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

42. (Withdrawn) The process according to Claim 41, wherein 825 parts by volume of water are introduced in step (i).

43. (Withdrawn) The process according to Claim 32, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

44. (Withdrawn) The process according to Claim 43, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

45. (Withdrawn) The process according to Claim 43, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

46. (Original) A pharmaceutical composition according to Claim 1, obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

47. (Original) The pharmaceutical composition according to Claim 46, wherein the process further comprises a filtration step following step (i) or (ii).

48. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

49. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

50. (Original) The pharmaceutical composition according to Claim 48, wherein step (i) of the process is performed with stirring.

51. (Original) The pharmaceutical composition according to Claim 50, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

52. (Original) The pharmaceutical composition according to Claim 46, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

53. (Original) The pharmaceutical composition according Claim 46, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to

from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

54. (Original) The pharmaceutical composition according to Claim 53, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

55. (Original) The pharmaceutical composition according to Claim 48, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

56. (Original) The pharmaceutical composition according to Claim 55, wherein 825 parts by volume of water are introduced in step (i) of the process.

57. (Original) The pharmaceutical composition according to Claim 46, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

58. (Original) The pharmaceutical composition according to Claim 57, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

59. (Original) The pharmaceutical composition according to Claim 57, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

60. (Original) The pharmaceutical composition according to Claim 46, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

61. (Original) The pharmaceutical composition according to Claim 60, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

62-64. (Cancelled)

65. (New) A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, wherein administering cladribine is accompanied by administering one or more additional active ingredients for treating the cladribine-responsive condition.

66. (New) The method according to Claim 65, wherein the complex is saturated with cladribine.

67. (New) The method according to Claim 65, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

68. (New) The method according to Claim 66, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

69. (New) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

70. (New) The method according to Claim 66, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

71. (New) The method according to Claim 67, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

72. (New) The method according to Claim 68, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

73. (New) The method according to Claim 65, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

74. (New) The method according to Claim 69, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

75. (New) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

76. (New) The method according to Claim 67, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

77. (New) The method according to Claim 73, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

78. (New) The method according to Claim 73, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

79. (New) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

80. (New) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

81. (New) The method according to Claim 65, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

82. (New) The method according to Claim 75, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

83. (New) The method according to Claim 65, wherein the cladribine-responsive condition is multiple sclerosis.

84. (New) The method according to Claim 75, wherein the cladribine-responsive condition is multiple sclerosis.

85. (New) The method according to Claim 77, wherein the cladribine-responsive condition is multiple sclerosis.

86. (New) The method according to Claim 83, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

87. (New) The method according to Claim 84, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group

consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

88. (New) The method according to Claim 85, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

REMARKS

Entry of the foregoing and further examination and consideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks that follow.

FOREIGN PRIORITY

The Examiner's acknowledgment of the claim for foreign priority and receipt of all certified copies of the priority documents is noted, with appreciation. However, the priority claims herein are domestic priority claims, this application being a continuation of a prior application which was a national stage of a PCT application, itself claiming benefit of several U.S. provisional applications.

DRAWINGS

Applicants thank the Examiner for accepting the drawings filed herein.

OBJECTION TO THE SPECIFICATION

The disclosure has been objected to because the reference to the copending application has not been updated. The specification has been amended to include the patent number of the patent granted on the parent application.

Withdrawal of the objection is believed to be in order and is respectfully solicited.

INFORMATION DISCLOSURE STATEMENT

The acknowledgment of the Information Disclosure Statements filed January 7, 2011 and August 9, 2012 and consideration of the documents cited therein are noted, with appreciation.

STATUS OF CLAIMS

Claims 1-88 are now in this application. Claims 9-24, 32-45 and 62-64 have been withdrawn. Claims 1-8, 25-31 and 46-61 are under examination. Claims 62-64 have been cancelled in favor of new Claims 65-88, which read on the same invention as cancelled Claims 62-64.

DISCUSSION OF CLAIM AMENDMENTS

New Claims 65-88 have been added to replace cancelled Claims 62-64. They are drawn to the same subject matter, which has been withdrawn from consideration. These new claims are fully based on pages 24-25 of the as-filed specification.

It is apparent from the foregoing that no new matter has been introduced by these claim amendments.

DISCUSSION OF RESTRICTION REQUIREMENT

The restriction requirement has been made final. Nevertheless, the withdrawn claims has been maintained. It is Applicants' intention to keep the withdrawn claims

commensurate in scope with those being examined, so that the withdrawn claims can be rejoined when patentable subject matter has been found.

Although Claims 65-88 are drawn to the same invention as Claims 62-64, Applicants point out that these methods of treatment claims differ from Claims 17-24 in requiring an additional active ingredient. If as a result, the Examiner believes that Claims 65-88 could not be rejoined for examination herein with the elected claims, he is asked to so advise the Applicants so that a separate divisional application can be promptly filed.

CLAIM REJECTIONS- 35 U.S.C. § 103

Claims 1-8, 25-31 and 46-61 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz (U.S. Patent No. 6,194,395) in view of Baert (International Publication No. WO97/18839). It is submitted that this rejection cannot be maintained against any of the claims now in this application.

Schultz describes two kinds of cyclodextrin formulations of cladribine, i.e., "soluble aqueous formulations of cladribine with cyclodextrin solubilizers which are injectable in humans, as well as oral solid dosage forms containing a mixture of cladribine and cyclodextrins." (Emphasis added). (See col., 1, lines 6-10, of the Schultz patent.) Applicants do not dispute the fact that Schultz discloses hydroxypropyl-β-cyclodextrin (HPβCD), which is amorphous, but Schultz discloses crystalline cyclodextrins as well. Indeed, Schultz teaches aqueous formulations containing a cladribine/HPβCD complex in solution for injectable use. On the other hand, Schultz clearly teaches that their solid oral dosage forms are mixtures of

cladribine and cyclodextrin as set forth not only in col. 1, lines 8-10 ("oral solid dosage forms containing a mixture of cladribine and cyclodextrin") but also in col. 5, lines 50-64. Nowhere does Schultz teach a sold oral dosage form containing a complex. In col. 5, lines 50-64, it is indicated that the solid oral dosage forms may be prepared as disclosed in Baert; this is in fact the only method disclosed by Schultz for preparing the solid oral dosage forms. In col. 5, beginning at line 52, it is stated that "solid mixtures of the cyclodextrins with the active ingredient are prepared via melt-extrusion....the cladribine active ingredient and the cyclodextrins are mixed with other optional ingredients and then heated until melting occurs. The mixture is then extruded through an extruder having one or more nozzles." As set forth in col. 6 of Schultz, a typical oral dosage form has a formulation containing, as a milled extrudate, 1 mg to 15 mg of cladribine and 100 to 500 mg of cyclodextrin, and as excipients, 100 to 300 mg of microcrystalline cellulose, 10 to 200 mg of crospovidone, 1 to 5 mg of colloidal silicon dioxide and 2 to 10 mg of sterotex. Schultz does not disclose or suggest to the ordinary skilled pharmaceutical scientist solid oral formulation of cladribine/cyclodextrin complexes, as claimed herein.

As explained in detail below, Applicants respectfully direct the Examiner to a reference by Van Axel Castelli (hereinafter referred to as "Van Axel Castelli"). Van Axel Castelli explains that the characteristics of a complex and a physical mixture are distinctly different. Schultz's solid mixtures of cladribine and cyclodextrin cannot be assumed to be the same as Applicants' product, which is a complex cladribine-cyclodextrin complex. Even if the broad ratios of Schultz's mixtures encompass the

ratios in Applicants' complexes, having the same ratio does not give a physical mixture the same properties as a complex, a fact which is clearly shown by Van Axel Castelli.

Also, Baert, which is incorporated by reference in Schultz, for its melt-extrusion method of making solid oral dosage forms, describes amorphous materials and solid solutions but does not teach or suggest that its solid dosage form products include amorphous cyclodextrin-drug complexes. On the contrary Baert teaches:

(a) Prior art problems are solved by Baert by the use of a melt-extrusion process to form solid mixtures comprising one or more cyclodextrins and insoluble active ingredients (Emphasis added; see page 3, lines 7-9).

(b) The compounds suitable for use in Baert's process "are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said one or more active ingredients with the cyclodextrin or cyclodextrins" (page 4, lines 5-7).

(c) Baert teaches that the characteristics of their products are different from those of a product obtained in water, since it is stated on page 6, lines 15-19:

> It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

(d) Baert's process uses very high temperatures; note Table 1 on page 12, where several different drugs are mixed with HPβCD and melt-extruded, with

temperatures of around 280°C being used and the products in every case, as noted on page 13, lines 5-6, being solid solutions.

(e) Baert does not mention cladribine; indeed, Applicants have previously shown that cladribine is known to decompose at the high temperatures used by Baert and thus cladribine falls in the group of compounds Baert teaches are unsuitable for use in their process [point (b) above].

(f) Baert in no way teaches or suggests that its products contain complexes.

The Examiner correctly states that the Schultz patent incorporates by reference the method of making their solid oral dosage form by utilizing the melt-extrusion process of Baert. The Baert process, as noted above, is carried out by mixing the cyclodextrin and the active ingredient, heating until melting one of the components, forcing the mixture through one or more nozzles, and cooling until the mixture solidifies (page 5, line 24-29). Milling may follow. The term "melting" is used broadly by Baert and includes transition to a glass; in particular cases, one component melts and the other dissolves therein forming solid solutions (page 5, lines 8-12). The extruded material may contain amorphous material or a solid solution (page 7, line 35 to page 8, line 7). While amorphous products are of interest, those which are mainly a solid solution are preferred (page 8, lines 11-23). Whether or not the products are amorphous, however, they are not taught to be complexes. In Table 1, on page 30, several different mixtures of hydroxypropyl-β-cyclodextrin and selected drugs were subjected to the Baert process. As noted on page 13, lines 5-6, in every case, the mixture using this

cyclodextrin gave a solid solution. The Examiner will note from Table 1 that the temperatures used, regardless of the identity of the drug, went as high as 292°C., with the temperatures for the itraconazole/HPβCD mixtures reaching 279°C-280°C. According to *The Merck Index* (copy of excerpt enclosed), itraconazole melts at 166.2°C while HPβCD melts at 278°C according to *LookChem* (copy of excerpt also attached).

The only solid dosage form envisioned by Schultz is a melt-extrusion product of cladribine and cyclodextrin prepared according to Baert. There is no evidence that such a product was ever prepared. Indeed, cladribine melts at 220-235°C with decomposition; see the enclosed excerpt from *Linscott's Directory* (copy attached) as well as that from *The Merck Index* (also enclosed). Thus, cladribine decomposes well below the 278°C melting point of HPβCD and well below the temperature used by Baert for their melt extrusion; cladribine is therefore not suitable for the Baert process, according to Baert's teaching that suitable compounds show no appreciable decomposition at the temperature they use (point b above).

Furthermore, Baert's teaching on page 6 that their melt-extrusion process affords different products than when their solids are first brought into contact with water (point c above) militates against the Examiner's finding that a cladribine/cyclodextrin product prepared by Baert's process is inherently the same as Applicants' product, which is, in fact, prepared by first contacting cyclodextrin with water. Indeed, it is the use of water that enables the formation of cyclodextrin-drug complexes; it is by complex formation that the water solubility of many drugs has been previously improved. There is no teaching by Baert that would lead one of ordinary skill to conclude that Baert et al made

solid complexes; indeed, Baert specifically teaches on page 6 that their products are different from products obtained by first dissolving cyclodextrin and drug in water. Thus, a melt-extrusion product of cladribine and cyclodextrin cannot inherently contain Applicants' product which comprises a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein. Applicants' product is prepared by preparing the complex in water; Baert teaches obtaining a different product than one that can be obtained from water; moreover, Applicants' process uses temperatures up to only about 80°C, far below the decomposition temperature for cladribine and far below the temperatures used by Baert. See Claims 32-45 herein. It is only by ignoring the teachings of Baert and by ignoring the Van Axel Castelli data that the Examiner can conclude that the Schultz product of the Baert process would inherently be Applicants' product. Indeed, Applicants have provided data in the form of the Van Axel Castelli article which clearly proves the difference between a mixture and a complex having the same ratio of ingredients.

The unsuitability of Baert's temperatures and hence for the Baert process, as applied to cladribine with cyclodextrin, specifically with HPβCD, is furthermore proved by data in Van Axel Castelli, as discussed in more detail below.

Also, to provide background with respect to drug/cyclodextrin complexation, Applicants bring to the Examiners' attention, the Loftsson and Brewster cyclodextrin review article previously made of record; see Loftsson and Brewster, "Pharmaceutical Application of Cyclodextrins. 1. Drug Solubilization and Stabilization," *Journal of Pharmaceutical Sciences*, Vol. 85, No. 10, pp. 1017-1025, 1996, American Pharmaceutical Association and the American Chemical Society, US. The Loftsson and Brewster review article shows that it was known in the art that:

(a) Cyclodextrin/drug complexation typically is carried out in aqueous media, not by mixing in the absence of water (page 1020, left column, first full paragraph).

(b) This complexation involves many different forces (van der Waals, hydrogen bonding, etc.) and the use of water is essential to the formation of complexes (page 1018, right column, second full paragraph to page 1020, left column, noting in particular the mention of release of water molecules from the cyclodextrin cavity as a driving force for drug-cyclodextrin complex formation).

(c) The complexes have different properties from mere physical mixtures of drugs and cyclodextrins, for example in terms of drug solubilization and drug stabilization (pages 1020-1024), a fact shown for HPβCD and cladribine in Van Axel Castelli discussed below.

(d) Amorphous cyclodextrins such as HPβCD have almost countless isomeric and variably substituted forms and upon complexation result in amorphous

products which are mixtures of countless complexes (page 1018, left column, line 12 from the bottom, to page 1018, right column line 2).

Applicants also take the position that the use of cladribine in Baert's melt extrusion product is inappropriate because of the fact that the decomposition temperature of cladribine is lower than the Baert process's temperature.

Furthermore, the experimental data in Van Axel Castelli and discussed below prove that cladribine and an amorphous cyclodextrin such as HPβCD do not form an eutectic mixture. Rather, Van Axel Castelli as discussed below, shows that cladribine, whether in a complex or in a mixture with HPβCD, decomposes at temperatures far below those used for this cyclodextrin in the Baert process.

Turning to Van Axel Castelli, a further copy of which is provided herewith for the Examiner's convenience, the following additional remarks are offered:

Van Axel Castelli shows that an inclusion complex of cladribine and 2-hydroxypropyl-β-cyclodextrin has properties that are different from those of the cyclodextrin, those of cladribine and those of physical mixtures of the cyclodextrin with cladribine. These can be summarized as follows:

(a) Thermo gravimetric analysis (TGA) was conducted over the temperature range from 25°C to 360°C for (a) cladribine, (b) HPβCD, (c) their inclusion complex and (d) their physical mixture and the results are shown in Fig. 2. Fig. 2a, the TGA curve for cladribine itself, shows decomposition of cladribine starting at about 200°C. Fig. 2b, the TGA curve for HPβCD, shows a mass loss of 6% at 30°C to about 140°C, due to dehydration, and decomposition at about 300°C. Fig. 2c, the TGA curve

for the cladribine/HPβCD complex, shows water loss between 20°C and 100°C and a decomposition process starting at about 250°C. Fig. 2d, the TGA curve for the cladribine plus HPβCD physical mixture, shows a multi-stage decomposition pathway; the first decomposition stage between room temperature and 100°C is due to loss of water from the cyclodextrin, whereas the second decomposition stage, observed at temperatures above 200°C, is due to the decomposition of cladribine. Fig. 2d also shows that heating the mixture to high temperatures does not lead to complexation but rather to decomposition of cladribine. Comparing the TGA for the complex with that of the physical mixture shows a slower degradation for the complex than for the mixture. Nevertheless, cladribine, whether in a complex or in a mixture with HPβCD, decomposes at temperatures far below those used for HPβCD-containing products in Baert's processes.

(b) Differential scanning calorimetry (DSC) analysis was conducted and the results shown in Fig. 3 for (a) cladribine, (b) HPβCD, (c) cladribine/HPβCD complex, (d) cladribine plus HPβCD physical mixtures, and (e) cladribine plus HPβCD kneading product. The authors note that the DSC trace of cladribine shows two endothermic events (Fig. 3a), the first at 206.3°C being close to the cladribine decomposition onset temperature and corresponding to the melting transition, and the second at 211.9°C, which is during the decomposition process, and probably is due to a decomposition product of cladribine. The DSC profile for the cyclodextrin (Fig. 3b) confirms an endothermic event corresponding to water loss from about 40°C to about 100°C. The authors further note that the DSC curves of the inclusion complex (Fig. 3c), physical

mixture (Fig. 3d) and kneading product (Fig. 3e) all show a broad thermal event from about 40 to 140°C, due to water loss in the cyclodextrin. In addition, the physical mixture and the kneading product are observed to feature two endothermic events around 200°C; these can be attributed to free cladribine in the mixture and kneading product. In contrast, Fig. 3c, the DSC trace for the complex, shows only one endothermic event, which occurs in the high temperature region, at 234.5°C; this is considerably higher than the degradation onset of pure cladribine around 200°C (Fig.2a), while the latter also characterizes the mixtures. As noted by the authors, the absence of thermal events typical of pure cladribine shows a loss of cladribine crystalline character for the complex. This also confirms DSC data for the products of instant Examples 1 and 2 reported on page 31 of the instant specification and correlates well with Applicants' x-ray diffraction traces for the products of Examples 1 and 2 reported on page 31 of the specification, where no peaks for crystalline cladribine were found in the complexes;

(c) FT-IR and FT-Raman spectroscopy were also recorded by Van Axel Castelli. In Figures 5 and 6, the FT-IR and FT-Raman spectra of cladribine alone (a), cladribine/cyclodextrin physical mixture (b), cladribine/cyclodextrin complex (c) and cyclodextrin alone (d) were compared. The authors indicate that the IR spectrum of the physical mixture (Fig. 5b) can be interpreted as the sum of the spectra for pure crystalline cladribine (Fig. 5a) and pure HPβCD (Fig. 5d), also supported by Fig. 6. The authors continue:

> In contrast, both IR and Raman spectra of the inclusion complex show clear differences with respect to those of the physical mixture. In particular, markers of the crystalline phase of cladribine (arrows on Figs. 4 and 5) cannot be found in the spectra of the inclusion complex.

The authors further find that their data suggest that, when part of an inclusion complex, cladribine is present in a different (non-crystalline) phase relative to that of pure crystalline cladribine and that direct interaction between cladribine molecules is prevented. Further, they note that the amorphous phase has to be attributed to the formation of molecular complexes where the interaction between cladribine and HPβCD shields cladribine molecules, thus preventing crystallization.

(d) Van Axel Castelli also used nuclear magnetic resonance spectroscopy to better understand the molecular interactions in the cladribine/cyclodextrin complex. To obtain direct proof of complex formation, the authors conducted a 2D ROESY experiment, the results of which showed a typical inner portion of HPβCD, confirming that a host-guest inclusion complex had formed between cladribine and HPβCD. Further, the authors conducted ^{13}C CP-MAS NMR experiments and reported the spectra in Fig. 10 for cladribine (a), cladribine + HPβCD physical mixture (b) and cladribine/ HPβCD complex (c). In the cladribine spectrum (Fig. 10a), the authors observed sharp peaks due to cladribine's high degree of crystallinity. The spectrum for the physical mixture (Fig. 10b) corresponds to the sum of the spectra of the two components, with no resonance peaks or line broadening, showing no intermolecular interaction in the mixture, the solid being composed of distinct ordered domains of each component. In the spectrum for the complex, no shift in the HPβCD

signals are detected, whereas the cladribine resonances are broadened and only slightly detectable. The authors note that this indicates that no crystalline domains of cladribine are present.

(e) Van Axel Castelli also conducted DSC and TGA thermal profiles for tablets of the cladribine/ HPβCD complex and found them comparable to those for the cladribine/ HPβCD complex itself. Moreover, even stressed tablets showed no notable differences in the DSC thermal profile, which demonstrated that they were storage stable even under less than ideal conditions.

(f) Van Axel Castelli concludes that thermal analyses, vibrational analyses, and solid-state NMR all indicate that cladribine behaves differently when in the complex compared with the physical mixture or kneading product, while ROESY provides evidence for the existence of an internal complex between cladribine and HPβCD. They further conclude that tablets of the complex are not affected by their manufacturing from the complex itself and are storage stable. These tablets have been used in a successful clinical trial for oral treatment of patients with MS (CLARITY trial).

In summary, Applicants submit that the obviousness rejection based on Schultz in view of Baert is untenable and should be withdrawn. The data provided by Van Axel Castelli conclusively show that cladribine, whether alone, in a physical mixture with HPβCD, or even in a cladribine/HPβCD complex, decomposes at temperatures far lower than those used by Baert for melt extruding drugs with the same cyclodextrin. The data further show that heating a physical mixture of cladribine with HPβCD to high temperatures does not result in a complex of cladribine and in fact the cladribine in the

mixture decomposes long before the melting point for HPβCD is reached. Thus, the Baert process is not suitable for making a melt extrudate of cladribine with hydroxypropyl-β-cyclodextrin and moreover such a product prepared according to Baert would not contain a complex of cladribine with the cyclodextrin as claimed in this application. The Schultz oral dosage form prepared by the Baert process simply cannot contain a cladribine/cyclodextrin complex.

Applicants emphasize that Baert melt-extrusion product is not one obtained by complexation in water; Baert teach their melt-extrusion product is different from a product whose preparation begins by dissolving the drug and cyclodextrin in water. Therefore, any product that Schultz might produce from cladribine and cyclodextrin subjected to Baert's melt extrusion product cannot be the same as Applicants' complex cladribine-cyclodextrin complex which must be obtained from an aqueous solution which is treated in a specific manner. Baert never suggests that they obtain a complex by their melt-extrusion process, much less one meeting the requirements of Applicants' claims. Indeed, Baert emphasize that their process, which is different, affords a different product than that obtained by first dissolving the drug and cyclodextrin. Likewise, Applicants emphasize that Applicants' process is strikingly different from Baert's process and thus logically would not afford the product which Schultz would have expected to obtain by subjecting cladribine and cyclodextrin to Baert's process. Moreover, Applicants have formed a very special complex which contains a large amount of cladribine as an amorphous inclusion complex and as amorphous free cladribine associated with the cyclodextrin as a non-inclusion complex. Note too that

the free cladribine associated with the non-inclusion product is amorphous, in contrast to the cladribine starting material, which is crystalline. Note also that Applicants produce their product by first complexing in water at temperatures of from about 45°C to about 80°C, far below the temperatures used by Baert. Cladribine actually decomposes at temperatures below that used by Baert.

It is clear from the foregoing that a molecular inclusion complexation process, let alone the particular inclusion process utilized by Applicants to form their unique complex cladribine-cyclodextrin complex, is not inherent in Baert's melt extrusion process and that Baert's process gives a different product. To hold otherwise would be to ignore Baert's own teachings. Claims 46-61 are drawn to a product-by-process. These claims depend, directly or indirectly, from Claim 1 and thus include all of the features in the combination of features defined in Claim 1. Applicants have shown that the composition of Claim 1 is free of the art, therefore, the product-by-process claims are also patentable over the art for at least the reasons that Claim 1 is patentable.

For at least the reasons set forth above, withdrawal of the § 103 rejection is in order and is earnestly solicited.

DOUBLE PATENTING REJECTION

Claims 1-8, 25-31 and 46-61 have been rejected on the ground on non-statutory double patenting as being unpatentable over Claims 1-28 of U.S. Patent No. 7,888,328. The Examiner has erred in issuing what appears to be a "same invention" double patenting rejection, which would only be proper if the claims were of identical scope to

those granted in the '328 patent. The instant claims are broader than those granted in the parent, therefore the double patenting "same invention" rejection is improper. Applicants are willing to file a terminal disclaimer with respect to the '328 patent to obviate an obviousness-type double patenting rejection, but such a rejection does not appear to have been made. There is no such thing as an "anticipation-type nonstatutory double patenting rejection." There are only two common types of double patenting rejections: 1) a "same invention" type double patenting rejection based on 35 U.S.C. § 101, which is statutory; and 2) a nonstatutory-type double patenting rejection prohibiting claims in a second patent not patentably distinguishing from claims in a first. This case fits in the second category, and the rejection clearly can be obviated by the filing of a terminal disclaimer of the commonly owned patent and application. An uncommon type of double patenting situation arose in *In re Schneller* but the first situation there is completely different than here. Moreover, in that case, the applicant had not filed a terminal disclaimer, whereas here an electronic terminal disclaimer has been filed today and accepted by the USPTO. It is also pointed out that Applicants did present claims corresponding to those herein in the parent application, so the Examiner's further statement relying on *In re Schneller is simply incorrect. Moreover, as noted, in In re Schneller, no terminal discaimer had been filed.*

CONCLUSION

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments,

reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 19-3140. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

DENTONS US LLP

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Attachments:

"Cladribine", The Merck Index, (2001), pp. 407-408, Thirteenth Edition, Merck & Co., Inc., Whitehouse Station, NJ

"Itraconazole", The Merck Index, (2001), p. 938, Thirteen Edition, Merck & Co., Inc. Whitehouse Station, NJ

"Hydroxypropyl-beta-cyclodextrin, CAS No. 94035-02-6" *LookChem*, http://www.lookchem.com/cas-940/94035-02-6.html, September 23, 2008

"Non-antibody Products (Kits, Proteins, Microbial Antigens, Tissues, Services, etc.) *Linscott's Directory of Immunological & Biological Reagents*, http://www.linscottsdirectory.com/browse/products/page:36, Records 1,751-1,800 of 130,353, September 11, 2008

Characterisation of an Inclusion Complex Between Cladribine and 2-Hydroxypropyl-β-Cyclodextrin

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ABSTRACT: Parenterally administered cladribine (2-chloro-2′-deoxyadenosine) has demonstrated promising efficacy and safety in clinical trials in patients with multiple sclerosis (MS). An oral formulation of this small molecule would be an attractive option for patients. Here, we describe the chemical characterisation of the inclusion complex between cladribine and the drug carrier molecule 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD). Several techniques were used to analyse the complex both in solution and in the solid state. These analyses provided evidence that the inclusion complex cannot be simply reduced to the sum of the two species, as it shows behaviour different from that of the physical mixture of the two components. Furthermore, solution nuclear magnetic resonance spectroscopy demonstrated the existence of an inclusion complex between cladribine and 2-HP-β-CD. Importantly, analysis of a tablet formulation demonstrated that the chemical characteristics of the inclusion complex are not affected by the manufacturing process, and that the complex is stable during storage. This tablet formulation is currently under investigation for the treatment of patients with MS.
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Keywords: cladribine; cyclodextrins; inclusion compounds; FT-IR; NMR spectroscopy; thermal analysis; oral drug delivery

INTRODUCTION

All currently available treatments for multiple sclerosis (MS) are administered parenterally, which is inconvenient and can be associated with localised pain.[1] An oral agent would be an attractive option for patients, and a number of oral therapies are currently in development for the treatment of MS. Cladribine (2-chloro-2′-deoxyadenosine), an analogue of adenosine (Fig. 1), is a preferential lymphocyte-depleting therapy that targets both resting and proliferating lymphocytes.[2,3] Cladribine is licensed for the treatment

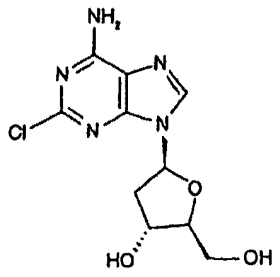
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Cladribine



2-HP-β-CD

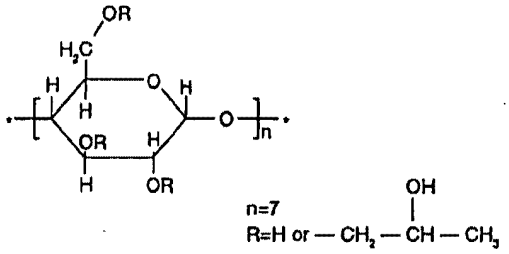


Figure 1. Chemical structures of 2-chloro-2′-deoxyadenosine (cladribine) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD).

of hairy cell leukaemia and B-cell chronic lymphocytic leukaemia, and has shown promising efficacy and a good safety profile in patients with MS (particularly patients with the relapsing–remitting form of the disease) when administered by intravenous infusion or subcutaneous injection.[4–8] As cladribine is a small molecule (molecular weight = 285.7 Da), it is an ideal candidate for development as an oral tablet formulation.

Cyclodextrins (CDs) are rationally designed drug carriers capable of modifying the physical, chemical and biological properties of drug molecules through the formation of inclusion complexes.[9–25] In general, hydrophilic CDs are employed to enhance the solubility and dissolution rate of poorly water-soluble drugs, whereas hydrophobic CDs are used to slow the dissolution rate of water-soluble drugs.[9,21,22] Advanced controlled release can be achieved by a combination of hydrophilic and hydrophobic CDs or pharmaceutical additives.[25] 2-Hydroxypropyl-β-cyclodextrin (2-HP-β-CD; Fig. 1) is a highly water-soluble CD, which has been used as an encapsulating agent for a variety of drugs, such as ibuprofen,[12] meloxicam,[16] tanshinone compounds[19] and ketoprofen,[12,20] among others. The formation of host–guest inclusion complexes between pharmacologically active small organic molecules and 2-HP-β-CD has been shown to improve the solubility, stability and bioavailability of these molecules. It has also been proposed that formation of a 2-HP-β-CD complex of cladribine to increase its water solubility may produce an orally bioavailable formulation of this drug.[26]

In this article the characterisation of the inclusion complex of cladribine with 2-HP-β-CD, both in solution and in the solid state, is reported. Analytical methods used include thermal analysis, mass spectrometry, Fourier-transform infrared (FT-IR) spectroscopy, FT-Raman and nuclear magnetic resonance (NMR) spectroscopy.

MATERIALS AND METHODS

Materials

Cladribine, 2-HP-β-CD and the cladribine/2-HP-β-CD inclusion complex[26] were obtained from Ivax Pharmaceuticals (Waterford, Ireland). The physical mixture of cladribine and 2-HP-β-CD was prepared by mixing the two components with a 1:1 molar ratio and subsequent homogenisation. Kneading samples were prepared[27] by adding a solution of methanol/water 50:50 (v/v) to the physical mixture to obtain a homogeneous paste. The cladribine/2-HP-β-CD tablet formulation was obtained from Ivax Pharmaceuticals and analysed by thermo gravimetric analyses (TGA) and differential scanning calorimetry (DSC). 'Stressed' tablets were produced by heating for 2 weeks at 40°C and 75% relative humidity.

Thermo Gravimetric Analysis

TGA was conducted using a TA Q-500 apparatus (TA Instruments, New Castle, DE). Samples were heated at a rate of 10°C/min, from 30 to 350°C in a dynamic nitrogen atmosphere.

Differential Scanning Calorimetry

DSC measurements were made on a TA Q-1000 differential scanning calorimeter (TA Instruments) using an aluminium nonhermetic pan. The heating rate was 10°C/min in the range of 20–300°C.

FT-IR and FT-Raman Spectroscopy

FT-IR and FT-Raman spectra of pure samples of cladribine, and the cladribine/2-HP-β-CD physical mixture and inclusion complex, were analysed.

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Samples were analysed in the solid state (sample as prepared, physical mixture, or after kneading) or in dimethyl sulfoxide (DMSO) solution. FT-IR spectra of solution samples were recorded on a Nicolet NEXUS (ThermoElectron, Waltham, MA) spectrometer in ATR mode ("SMART performer" module), in the spectral region from 4000 to 650 cm^{-1}. Each experiment was performed with 512 scans at a resolution of 2.0 cm^{-1}. Solid samples were analysed as pellets, prepared by grinding a few milligrams of sample with 40 mg of KBr and then compressing the powder at a pressure of 10 ton/cm^2. FT-IR infrared spectra of solid samples were recorded on a Nicolet NEXUS FTIR spectrometer (ThermoElectron). For each spectrum, 256 scans were collected with a resolution of 1 cm^{-1} in the spectral range 400–4000 cm^{-1}. Raman experiments were carried out using a Nicolet NXR 9650 instrument (ThermoElectron).

Electrospray Mass Spectrometry

Mass spectra were acquired on a triple quadrupole spectrometer equipped with a turbo-ion spray source (Q-Trap from Applied Biosystems, Foster City, CA). Samples were introduced into the source at a flow rate of 10 μL/min using a syringe pump. All the spectra were acquired in positive ion mode in a spectral range from 100 to 1700 *m/z*. The ionisation voltage was set at 4500 V and the declustering potential was set to 30 V.

Nuclear Magnetic Resonance

NMR experiments were carried out at 298 K on a Bruker Avance500 spectrometer (Bruker BioSpin, Rheinstetten, Germany), operating at 500.13 MHz for ^1H. Spectra in solution were performed using a 5 mm PABBI probe with a *z*-gradient unit. Samples for NMR experiments in solution were prepared by dissolving ~15 mg of cladribine, 2-HP-β-CD, or the inclusion complex in 700 μL of D_2O or d_6-DMSO. ^1H NMR spectra in d_6-DMSO were performed with a pulse width (pw, 90°) of 6.8 μs. ^1H NMR spectra in D_2O were performed applying a sequence with water suppression using excitation sculpting with gradients;[28] pw (90°), 7.2 μs; sculpting pw, 2 ms. ^1H-^1H 2D experiments (COSY [COrrelation SpectroscopY], TOCSY [TOtal Correlation SpectroscopY], NOESY [Nuclear Overhauser Enhancement SpectroscopY] and ROESY [Rotating frame Overhauser Enhancement SpectroscopY]) were carried out in States-TPPI phase sensitive mode, using excitation sculpting with gradients for water suppression[28] in conditions analogous to those applied for 1D spectra. Time domain (TD){F2}, 2K; TD{F1}, 512; sweep width (SW), 10 ppm. ^1H-^1H TOCSY experiments were carried out with a mixing time of 40 ms, using an MLEV-17 sequence. In the case of ^1H-^1H ROESY experiments, a mixing time of 200 ms was set. Solid-state NMR spectra were performed with a MAS BB 4 mm probe. The sample-spinning rate was set at 5.0 kHz.

^{13}C cross-polarisation magic angle spinning (CP-MAS) NMR spectra were acquired with 3.20 μs proton 90° pw, 1.0 ms contact time, and 60 s recycle time. Chemical shifts are expressed in ppm downfield from tetramethylsilane. No internal reference was used in order to avoid binding interference with the CD.

RESULTS AND DISCUSSION

Thermo Gravimetric Analysis

The TGA profiles of cladribine, 2-HP-β-CD, their inclusion complex, and physical mixture from 25 to 360°C are presented in Figure 2. The TGA curve of cladribine indicates a decomposition process starting at about 200°C (Fig. 2a). In the case of 2-HP-β-CD, a mass loss of 6% was observed from 30°C to about 140°C, due to dehydration (Fig. 2b). The TGA of the cladribine/2-HP-β-CD inclusion complex showed water loss between 20 and 100°C

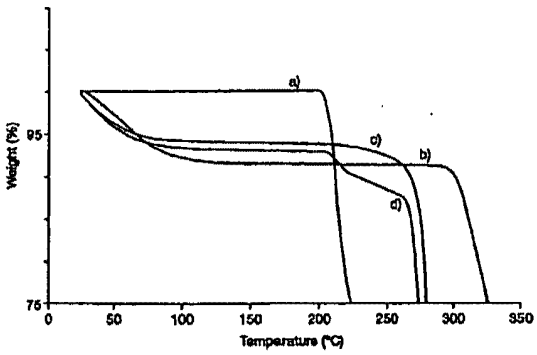


Figure 2. Thermo gravimetric analysis profiles from 25°C to 360°C for (a) cladribine; (b) 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD); (c) cladribine/2-HP-β-CD inclusion complex; and (d) cladribine plus 2-HP-β-CD physical mixture.

and a decomposition process starting at about 250°C (Fig. 2c). The decomposition temperature for the inclusion complex was significantly higher than the decomposition temperature observed for pure cladribine (250°C vs. 200°C, respectively). The TGA curve of the cladribine plus 2-HP-β-CD physical mixture shows a multi-stage decomposition pathway (Fig. 2d). The first stage between room temperature and 100°C is due to the water content loss of CD, whereas the second stage, observed at temperatures above 200°C, is due to the decomposition of cladribine. By comparing the decomposition stage of TGA for the complex and the physical mixture, it appears that the complex degrades slower than the mixture. The higher thermal stability of the complex is an indication of the onset of host–guest interactions.[29]

Differential Scanning Calorimetry

In order to better understand the thermal behaviour of the samples, DSC analysis was conducted (Fig. 3). The DSC trace of cladribine shows two endothermic events (Fig. 3a). The first endothermic event at 206.3°C is close to the cladribine decomposition onset temperature and corresponds to the melting transition. The second endothermic event, occurring at 211.9°C, that is during the decomposition process, is probably due to a decomposition product of cladribine. The DSC profile of 2-HP-β-CD confirms an endothermic event corresponding to the water loss (Fig. 3b). The DSC curves of the inclusion complex, physical mixture and kneading product all show a broad thermal event (from 40 to 140°C), due to water loss in the CD (Fig. 3c–e). In addition, the physical mixture and the kneading product feature two endothermic events around 200°C, which can be attributed to the free cladribine.

Remarkably, the DSC trace of the inclusion complex (Fig. 3c) shows only one endothermic event in the high temperature region, at 234.5°C, which is a temperature considerably higher than the degradation onset of pure cladribine (~200°C; Fig. 2a). The absence of thermal events typical of pure cladribine indicates a loss of cladribine crystalline character when it is involved in the complex. This represents indirect evidence for the formation of the cladribine/2-HP-β-CD inclusion complex.

FT-IR and FT-Raman Spectroscopy

The FT-IR and FT-Raman spectra of several samples were recorded to detect spectral signals (band frequencies and band intensities) that may reveal the existence of intermolecular interactions between cladribine and 2-HP-β-CD in the inclusion complex.

In Figure 4, the FT-Raman spectra of different samples of cladribine (as prepared, after kneading, and in solution) in the region 1700–200 cm^{-1} are reported. The FT-Raman spectra of the two solid-state samples (as prepared and after kneading) are practically coincident, indicating that the procedure adopted to prepare the complex does not affect the physical state of the molecule. In DMSO solution, cladribine molecules cannot

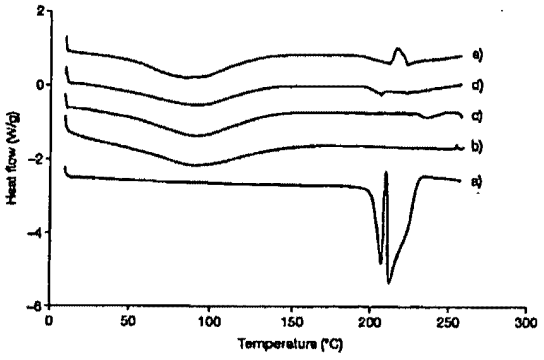


Figure 3. Differential scanning calorimetry profiles of (a) cladribine; (b) 2-HP-β-CD; (c) cladribine/2-HP-β-CD inclusion complex; (d) cladribine plus 2-HP-β-CD physical mixture; and (e) cladribine plus 2-HP-β-CD kneading product.

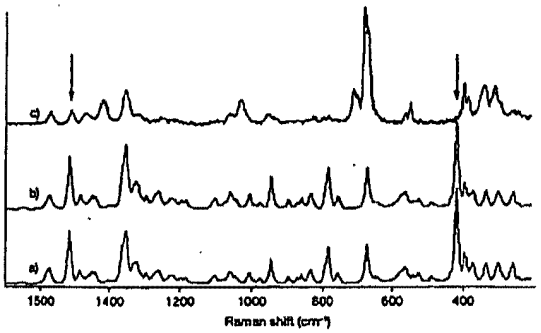


Figure 4. Fourier-transform Raman spectra of (a) cladribine as prepared; (b) cladribine after kneading; (c) cladribine in DMSO (after subtraction of DMSO spectrum). Arrows indicate peaks of interest referred to in the text.

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interact with each other because of the surrounding solvent, and the Raman spectrum undergoes drastic changes. For example, the Raman lines at 1513 and 413 cm^{-1}, characteristic of pure cladribine, strongly decrease in intensity in the spectrum of solution (see arrows on Fig. 4c).

The FT-IR spectrum of cladribine (as prepared) shows many sharp bands. In the high frequency region, it is possible to identify the O–H stretching band of isolated (free) OH bonds at 3542 cm^{-1} and the four well-defined N–H stretching bands in the region 3500–3150 cm^{-1} (see arrows on Fig. 5a).

Both Raman and IR spectra show very sharp vibrational bands for pure cladribine, indicating the molecules are in a structurally defined and regular environment (i.e. in a crystalline field). This observation supports the hypothesis (confirmed by NMR experiments, see below in the text) that pure cladribine forms a crystalline phase. Moreover, comparisons between solid samples and samples in DMSO solution indicate that the Raman spectroscopic signals at 1513 and 413 cm^{-1} can be used as markers of the crystalline phase of cladribine. The bands at 3542 cm^{-1} and 3500–3150 cm^{-1} in the IR spectrum also indicate the presence of a well-defined crystalline structure. In particular, the band observed at 3542 cm^{-1}, assigned to the stretching of free OH bonds, is in agreement with the crystal structure of cladribine as reported in the literature.[12] Mura et al.[12] noted the presence of OH bonds (one for each cladribine molecule), which do not form intermolecular hydrogen bonds.

In Figures 5 and 6, the FT-IR and FT-Raman spectra of cladribine, 2-HP-β-CD, their inclusion complex and physical mixture are compared. The

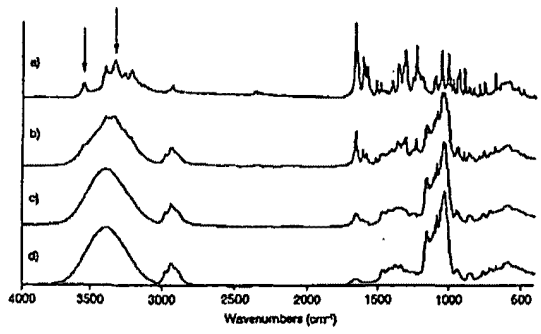


Figure 5. Fourier-transform infrared spectra of (a) cladribine as prepared; (b) cladribine plus 2-HP-β-CD physical mixture; (c) cladribine/2-HP-β-CD inclusion complex; and (d) 2-HP-β-CD. Arrows indicate peaks of interest referred to in the text.

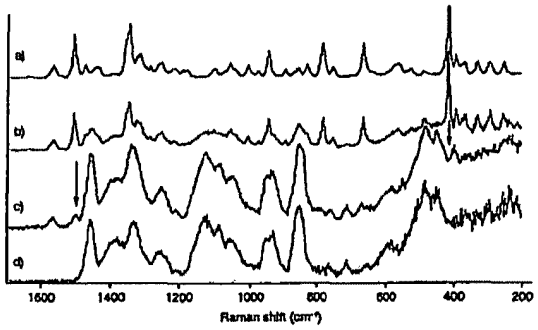


Figure 6. Fourier transform Raman spectra of (a) cladribine as prepared; (b) cladribine plus 2-HP-β-CD physical mixture; (c) cladribine/2-HP-β-CD inclusion complex; and (d) 2-HP-β-CD. Arrows indicate peaks of interest referred to in the text.

IR spectrum of the physical mixture in Figure 5 can be interpreted as the 'sum' of the spectra for pure cladribine and pure 2-HP-β-CD. This is a clear indication of the presence of two separate phases: crystalline cladribine and 2-HP-β-CD. The same conclusion is reached from the analysis of the FT-Raman spectra in Figure 6.

In contrast, both IR and Raman spectra of the inclusion complex show clear differences with respect to those of the physical mixture. In particular, markers of the crystalline phase of cladribine (arrows on Figs. 4 and 5) cannot be found in the spectra of the inclusion complex. Moreover, the FT-Raman spectral features indicated by arrows on Figure 6 (ascribed to cladribine in the inclusion complex) show similarities with those of cladribine in DMSO solution (see Fig. 4c). This suggests that, when part of the inclusion complex, cladribine is present in a different phase relative to that of pure (crystalline) cladribine, and that direct interaction between cladribine molecules is prevented. Therefore, it seems that 2-HP-β-CD acts in a similar way to a solvent, shielding each cladribine molecule from other molecules of the same species. Cladribine samples obtained by kneading show the same spectral markers of crystallinity observed in the sample as prepared (Fig. 4), indicating that the origin of this 'amorphous' phase cannot be explained by differences in methods of preparation for the inclusion complex and crystalline cladribine. The origin of the amorphous phase, therefore, has to be attributed to the formation of molecular complexes where the interaction between cladribine and 2-HP-β-CD shields cladribine molecules, thus preventing crystallisation.

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Electrospray Ionisation Mass Spectrometry (ESI-MS) Analysis

ESI-MS is a powerful tool for the study of non-covalent complexes of CDs.[30–33] The mild ionisation procedure allows the solution state structure of the complexes to be retained in the gaseous phase.[34] 2-HP-β-CD and the cladribine/2-HP-β-CD inclusion complex were analysed using ESI-MS.

The spectrum of 2-HP-β-CD (see Supporting Information) consists of a main distribution of single-charged ions, starting from *m/z* 1330 atomic mass units up to 1679 atomic mass units in which each peak is separated by 58 atomic mass units, corresponding to the 2-hydroxypropyl moiety. The spectrum reveals that 2-HP-β-CD is characterised by a degree of substitution, ranging from one to seven substitutions, in which the numerically most abundant species is CD substituted with four 2-hydroxypropyl groups. The ESI mass spectrum of the cladribine/2-HP-β-CD inclusion complex shows two main distributions (see Supporting Information). The first distribution, centred at *m/z* 1505 atomic mass units represents 2-HP-β-CD/Na^+ adducts. The second distribution, centred at *m/z* 790 atomic mass units, consists of double-charged ions assignable to 2-HP-β-CD. The ESI-MS spectrum of the cladribine/2-HP-β-CD complex shows some differences with respect to the spectrum of free CD. However, clear evidence of the presence of the inclusion complex is not observed. Probably the ionisation process, in this case, does not allow survival of the complex.

Nuclear Magnetic Resonance Spectroscopy

Several high-resolution 1D and 2D NMR experiments were carried out in order to better understand the molecular interactions in the cladribine/2-HP-β-CD inclusion complex. ^{1}H-NMR spectra of cladribine and 2-HP-β-CD in d_6-DMSO are reported in Figure 7a and b, respectively. The assignment of ^{1}H resonances of cladribine in d_6-DMSO is reported in Table 1. The assignment of ^{1}H resonances of 2-HP-β-CD in d_6-DMSO is rather complex, and ^{1}H resonances of 2-HP-β-CD in D_2O are presented in Table 1. The spectrum of 2-HP-β-CD in D_2O is simplified because of the chemical exchange of OH with deuterium atoms (Fig. 7c).

Assignments shown in Table 1 for proton resonances of 2-HP-β-CD in D_2O are based on

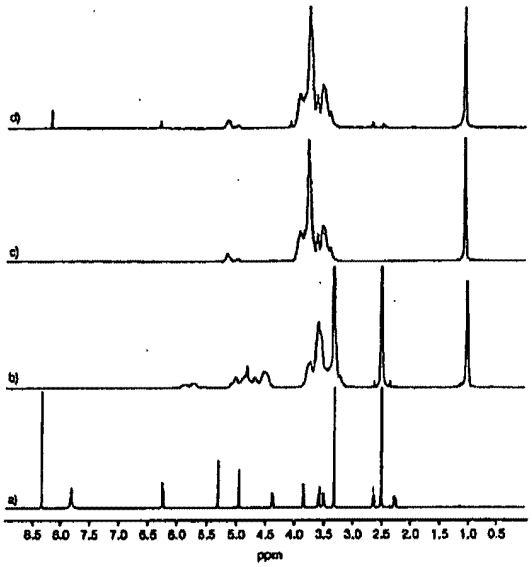


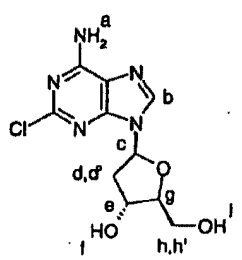
Figure 7. 500.13 MHz ^{1}H NMR spectra in solution: (a) CdA in d_6-DMSO; (b) 2-HP-β-CD in d_6-DMSO; (c) 2-HP-β-CD in D_2O with water suppression; (d) CdA/2-HP-β-CD complex in D_2O with water suppression.

the literature[35,36] and the analysis of several 2D NMR experiments,[37] namely, COSY, TOCSY and NOESY (see Fig. 8 and Supporting Information). The COSY pulse sequence gives rise to a 2D map in which cross-peaks appear between *J*-coupled protons. In the TOCSY experiment, cross-peaks are shown between all protons connected in a chain. The cross-peak intensity decreases with increasing distance between protons along the chain. Finally, the NOESY experiment gives correlation signals due to dipolar cross-relaxation between nuclei in a close spatial relationship. Cross-peak intensity is proportional to the distance between protons.

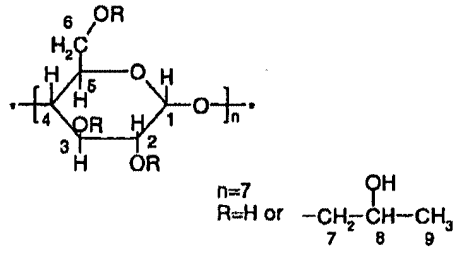
Two types of anomeric protons can be distinguished (due to regioisomers),[36] indicated as H1 and H1′ in Figure 8, resonating at 5.17 and 4.99 ppm, respectively. From the TOCSY experiment (Fig. 8) it is also possible to differentiate protons H2 and H3, from protons H2′ and H3′. It should be noted that for 2-HP-β-CD, inner protons (H3, 3′ and H5, 5′) show a downfield shift with respect to protons that are outside the cavity (H1, 1′, H2, 2′, H4, 4′ and H6, 6′). This observation is consistent with the literature.[35]

The ^{1}H NMR spectrum of the cladribine/2-HP-β-CD inclusion complex in D_2O is reported in

Table 1. Assignment of ^1H NMR resonances of cladribine and 2-HP-β-CD



Cladribine



2-HP-β-CD

Type	δ (ppm)	Multiplicity, J (Hz)
Cladribine in d_6-DMSO		
a	7.83	bs
b	8.35	s
c	6.26	dd (J = 7.3, 6.2)
d	2.64	ddd (J = 13.3, 7.3, 5.8)
d′	2.27	ddd (J = 13.3, 6.2, 3.3)
e	4.38	dddd (J = 5.8, 4.2, 3.3, 2.8)
f	5.31	d (J = 4.2)
g	3.85	dt (J = 4.6, 2.8)
h	3.59	ddd (J = 11.8, 5.4, 4.6)
h′	3.51	ddd (J = 11.8, 6.0, 4.6)
i	4.96	dd (J = 6.0, 5.4)
2-HP-β-CD in D_2O		
1	5.17	bs
1′	4.99	bs
2	3.40	m
2′	3.5	m
3	3.96	m
3′	3.86	m
4,4′	3.55	Overlapped to other signal
5,5′	3.80–3.72	Overlapped to other signals
6,6′	3.78	Overlapped to other signals
7	3.71,3.64, 3.53,3.46	m
8	3.94	m
9	1.08	bs

Figure 7d, and corresponding COSY and TOCSY maps are reported in the Supporting Information.

To obtain direct proof of complex formation, a 2D ROESY experiment was conducted. As with the NOESY experiments, protons that are spatially adjacent give rise to cross-peaks in ROESY spectra. An expansion of the ROESY map of the cladribine/2-HP-β-CD inclusion complex in D_2O is reported in Figure 9. In addition to the expected intramolecular cross-peaks, some intermolecular cross-peaks were observed in the spectra. In particular, cross-peaks between H3, H3′, H5 and H5′ of 2-HP-β-CD and protons d, d′ of cladribine indicate that cladribine and CD are in close proximity. This interaction involves a typical inner proton of 2-HP-β-CD, indicating that a host–guest inclusion complex has formed between cladribine and 2-HP-β-CD. The NOE experiment was used solely as a diagnostic tool and, therefore, no quantitative information about interaction strength was determined.

Solid-state behaviour was investigated by means of ^{13}C CP-MAS NMR experiments.[37] The ^{13}C CP-MAS spectra of cladribine, the cladribine plus 2-HP-β-CD physical mixture, and cladribine/2-HP-β-CD inclusion complex are reported in Figure 10. In the cladribine spectrum, sharp peaks due to its high degree of crystallinity are

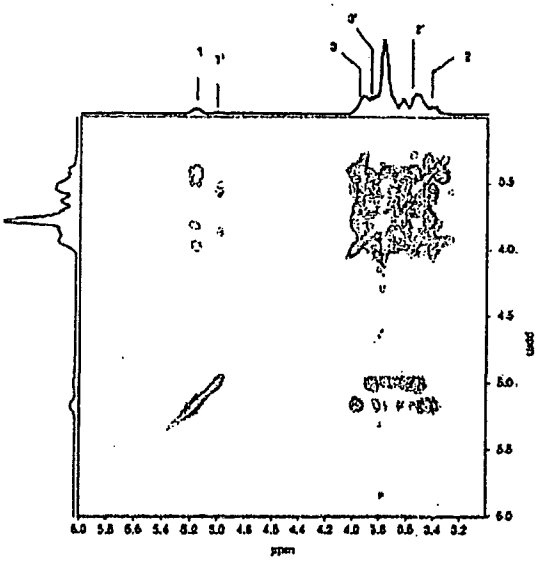


Figure 8. Enlarged region of the ^{1}H-^{1}H TOCSY NMR map of 2-HP-β-CD in D_2O. The assignment of resonances is reported in Table 1.

observed (Fig. 10a). The ^{13}C CP-MAS spectrum of the physical mixture corresponds to the sum of the spectra of the two components, cladribine and 2-HP-β-CD (Fig. 10b). No resonance shifts or line broadening are detected in this spectrum, clearly

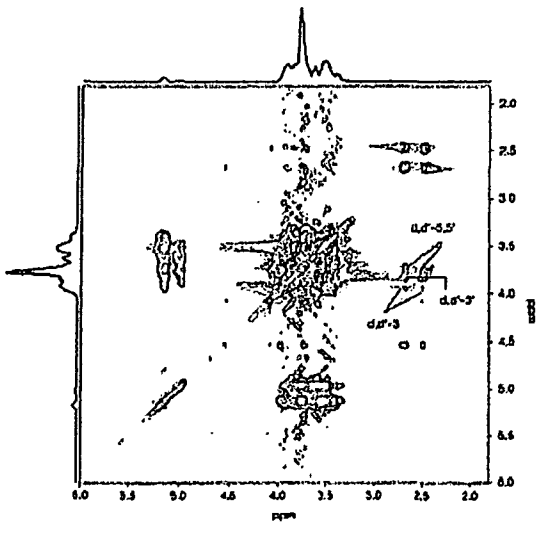


Figure 9. Enlarged region of the ^{1}H-^{1}H ROESY NMR map of CdA/2-HP-β-CD complex in D_2O. The correlation between protons d, d′ of CdA and inner protons H3, H3′, H5, H5′ of 2-HP-β-CD (see Table 1) is indicated.

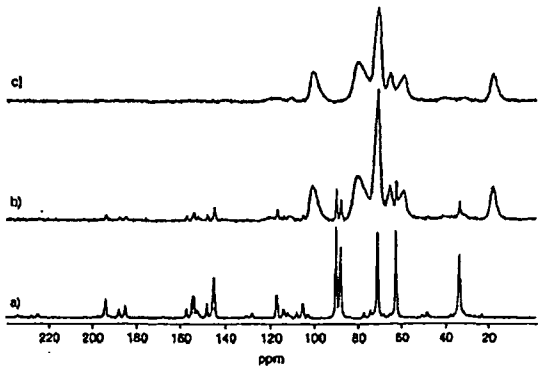


Figure 10. ^{13}C CP-MAS spectra of: (a) CdA; (b) CdA + 2-HP-β-CD physical mixture; (c) CdA/2-HP-β-CD complex.

indicating that no intermolecular interaction exists between cladribine and 2-HP-β-CD, and that the solid is composed of distinct ordered molecular domains of each component. Thus, solid-state properties of the mixture are to be considered simply as cladribine domains interspersed among domains of 2-HP-β-CD.

The ^{13}C CP-MAS spectrum of the cladribine/2-HP-β-CD inclusion complex reveals some interesting features (Fig. 10c). No chemical shift perturbation of 2-HP-β-CD signals is detected, whereas the cladribine resonances are broadened and only slightly detectable (see in particular the spectral region δ 20–50 ppm). This indicates that no crystalline domains of cladribine are present. In fact, these results show that the sample consists of cladribine dispersed at a molecular level in the 2-HP-β-CD solid.

Analysis of Cladribine/2-HP-β-CD Tablet Formulation

DSC and TGA thermal profiles for the cladribine/2-HP-β-CD tablet formulation were comparable with those for the cladribine/2-HP-β-CD inclusion complex sample (data not shown). This indicates that the cladribine/2-HP-β-CD inclusion complex is not affected by the manufacturing procedures used to prepare the tablet. Thermal analysis of the stressed tablet formulation showed no notable differences in DSC thermal profile but higher water content in the TGA profile, compared with the cladribine/2-HP-β-CD inclusion complex. This demonstrates that the complex is stable on storage.

DOI 10.1002/jps

CONCLUSIONS

This publication reports the first comprehensive chemical analysis of the cladribine/2-HP-β-CD inclusion complex, which provides indirect evidence for the presence of intermolecular interactions between cladribine and 2-HP-β-CD in this complex. Thermal analyses (both TGA and DSC), vibrational analyses (both FT-IR and FT-Raman), and solid-state NMR all indicate that cladribine behaves differently when in the inclusion complex compared with the physical mixture or the kneading product. Finally, detection of NOE cross-peaks due to the 2-HP-β-CD inner hydrogens (H3, 3′, and H5, 5′) characteristically located inside the CD cavity (ROESY) provides evidence for existence of an internal complex between cladribine and 2-HP-β-CD.

Importantly, analysis of the cladribine/2-HP-β-CD tablet formulation demonstrated that the chemical characteristics of the cladribine/2-HP-β-CD inclusion complex are not affected by the manufacturing process and that the complex is stable during storage. This tablet formulation is under investigation in an ongoing clinical programme as a once-daily, intermittent oral treatment for patients with MS (CLARITY [cladribine tablets treating multiple sclerosis orally] and ONWARD [oral cladribine added on to Rebif new formulation in subjects with active multiple sclerosis] studies).

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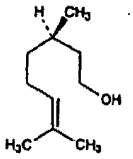
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α-citronellal. [141-26-4] 3,7-Dimethyl-7-octenal; rhodinal. Liquid bp_{14} 51°. n_D^{20} 1.4410. $[\alpha]_D^{20}$ +9.75°.
USE: In soap perfumes; insect repellent.

2354. β-Citronellol. [106-22-9] 3,7-Dimethyl-6-octen-1-ol; 2,6-dimethyl-2-octen-8-ol; citronellol; cephrol. $C_{10}H_{20}O$; mol wt 156.26. C 76.86%, H 12.90%, O 10.24%. *l*-Form is a constituent of rose and geranium oils. *d*-Form occurs in Ceylon and Java citronella oils. History: J. L. Simonsen, L. N. Owen, *The Terpenes* vol. I (University Press, Cambridge, 2nd ed, 1947). Prepn of (±)-form: Adams, Garvey, *J. Am. Chem. Soc.* 48, 477 (1926); Ofner *et al., Helv. Chim. Acta* 42, 2577 (1959). Prepn of (+)-form: Rienäcker, Ohloff, *Angew. Chem.* 73, 240 (1961); Naves, Tullen, *Helv. Chim. Acta* 44, 1867 (1961); Eschinazi, *J. Org. Chem.* 26, 3072 (1961); Rienäcker, *Chimia* 27, 97 (1973); C. G. Overberger, J. L. Weise, *J. Am. Chem. Soc.* 90, 3525 (1968); T. Sato *et al., Tetrahedron Letters* 1980, 3377. Prepn of (−)-form: Ohloff, *loc. cit.*; Rienäcker, *loc. cit.*; Shono *et al., Tetrahedron Letters* 1974, 1295; K. Mori, T. Sugai, *Synthesis* 1982, 752. Synthesis of (+) or (−)-form from isoprene: Hidai *et al., Chem. Commun.* 1975, 170. Stereospecific prepn via microbiological *(Saccharomyces cerevisiae)* reduction: P. Gramatica *et al., Experientia* 38, 775 (1982). Manuf: Woroch *et al.*; Bain; Webb, US 2990422; US 3005845; US 3028431 (1961, 1961, 1962, all to Glidden); Eschinasi, US 3052730 (1962 to Givaudan). Abs config of the (+)-form: Freudenberg, Hohmann, *Ann.* 584, 54 (1953); Freudenberg, Lwowski, *ibid.* 587, 213 (1954). NMR, HPLC determn of *R/S* enantiomer ratios: D. Valentine *et al., J. Org. Chem.* 41, 62 (1976). *See also* Rhodinol.



R-(+)-β-Citronellol

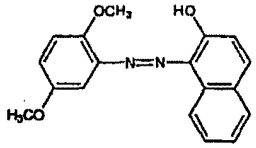
(+)-Form. Oily liquid, bp 224.5°, bp_{10} 108.4°, d_4^{20} 0.8550. n_D^{20} 1.4559. $[\alpha]_D^{20}$ +5.22°. Very slightly sol in water, miscible with with alcohol, ether.
(−)-Form. β-Rhodinol; Levocitrol. bp_{10} 108-109°. d_4^{15} 1.4576. $[\alpha]_D^{20}$ −4.76°.
(±)-Form. Dihydrogeraniol. $d_4^{23.5}$ 0.851. $n_D^{23.5}$ 1.454.
USE: In perfumery.

2355. Citrulline. [372-75-8] N^5-(Aminocarbonyl)-L-ornithine; δ-ureidonorvaline; α-amino-δ-ureidovaleric acid; N^5-carbamylornithine. $C_6H_{13}N_3O_3$; mol wt 175.19. C 41.13%, H 7.48%, N 23.99%, O 27.40%. $H_2NCONH(CH_2)_3CH(NH_2)$-COOH. An amino acid, first isolated from the juice of watermelon, *Citrullus vulgaris* Schrad., *Cucurbitaceae:* Wada, *Biochem. Z.* 224, 420 (1930); isoln from casein: Wada, *ibid.* 257, 1 (1933). Synthesis from ornithine through copper complexes: Kurtz, *J. Biol. Chem.* 122, 477 (1938); by alkaline hydrolysis of arginine: Fox, *ibid.* 123, 687 (1938); from cyclopentanone oxime: Fox *et al., J. Org. Chem.* 6, 410 (1941). Crystallization: Matsuda *et al.*, JP 71 174 (1971 to Ajinomoto), *C.A.* 74, 126056u (1971). Crystal and molecular structure: Naganathan, Venkatesan, *Acta Crystallogr.* 27B, 1079 (1971); Ashida *et al., ibid.* 28B, 1367 (1972). Use in asthenia and hepatic insufficiency: FR 2198739 (1974 to Hublot & Vallet), *C.A.* 82, 144952c (1975). Clinical trial in treatment of lysinuric protein intolerance: J. Rajantie *et al., J. Pediatr.* 97, 927 (1980); T. O. Carpenter *et al., N. Engl. J. Med.* 312, 290 (1985). Prisms from methanol + water, mp 222°. $[\alpha]_D^{20}$ +3.7° (c = 2). pK_1 2.43; pK_2 9.41. Sol in water. Insol in methanol, ethanol.
Hydrochloride. [34312-10-2] $C_6H_{13}N_3O_3.HCl$. Crystals, dec 185°. $[\alpha]_D^{22}$ +17.9° (c = 2).

Malate (salt). [54940-97-5] Stimol. $C_6H_{13}N_3O_3.C_4H_6O_5$; mol wt 309.27.
THERAP CAT: Treatment of asthenia.

2356. Citrullol. [1390-93-8] $C_{22}H_{38}O_4$; mol wt 366.53. C 72.09%, H 10.45%, O 17.46%. From fruit pulp of *Citrullus colocynthis* Schrad., *Cucurbitaceae:* Power, Moore, *J. Chem. Soc.* 97, 99 (1910); Power, Salway, *ibid.* 103, 399, 1022 (1913); Khadem, Rahman, *Tetrahedron Letters* 1962, 1137.
Crystals, mp 282-283°. uv max: 242, 272, 282 nm (log ε 2.85, 2.68, 2.68). Sol in pyridine; practically insol in usual organic solvents.
Diacetate. $C_{26}H_{42}O_6$. Crystals, mp 162°.

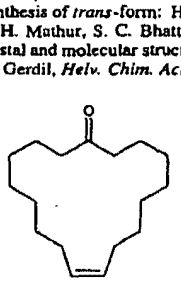
2357. Citrus Red 2. [6358-53-8] 1-[(2,5-Dimethoxyphenyl)azo]-2-naphthalenol; C.I. Solvent Red 80; C.I. 12156. $C_{18}H_{16}N_2O_3$; mol wt 308.33. C 70.12%, H 5.23%, N 9.09%, O 15.57%. Prepn: H. W. Elley, H. W. Daudt, US 2224904 (1940 to Du Pont). Metabolism: J. L. Radomski, *J. Pharmacol. Exp. Ther.* 134, 100 (1961); 136, 378 (1962). Toxicology: M. Sharratt *et al., Food Cosmet. Toxicol.* 4, 493 (1966). Review of carcinogenicity studies: *IARC Monographs* 8, 101-106. *See also Colour Index* vol. 4 (3rd ed., 1971) p 4033.



Crystals, mp 155-157°. Slightly sol in water; partially sol in ethanol and vegetable oils.
USE: To color orange skins.

2358. Civet. Zibeth. Unctuous secretion from receptacles between the anus and genitalia of both male and female civet cat. *Constit.* Civetone and similar compds.
Semi-solid, yellowish to brown unctuous substance; unpleasant, subacrid, bitter taste; fusible and burns without leaving much residue. Insol in water; partly sol in hot alcohol or in ether.
USE: As a fixative in perfumery.

2359. Civetone. [542-46-1] (*Z*)-9-Cycloheptadecen-1-one. $C_{17}H_{30}O$; mol wt 250.42. C 81.54%, H 12.07%, O 6.39%. 17-Membered macrocyclic musk, constituent of civet: Ruzicka, *Helv. Chim. Acta* 9, 230 (1926); Ruzicka *et al., ibid.* 10, 695 (1927). Occurs in nature as *cis*-form. Synthesis of *cis*-civetone: Stoll *et al., ibid.* 31, 543 (1948); J. Tsuji, T. Mondai, *Tetrahedron Letters* 1977, 3285; E. Seoane *et al., Chem. & Ind. (London)* 1978, 165. Synthesis of *trans*-form: H. Hunsdiecker, *Ber.* 77, 185 (1944); H. H. Mathur, S. C. Bhattacharyya, *J. Chem. Soc.* 1968, 114. Crystal and molecular structure of *cis*-civetone: G. Bernardinelli, R. Gerdil, *Helv. Chim. Acta* 65, 558 (1982).



(cis)-form

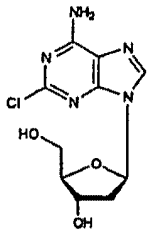
Crystals, mp 31-32°. Musky odor becoming pleasant in extreme dilns. d_4^{33} 0.917. bp_{742} 342°; bp_2 59°. $n_D^{23.4}$ 1.4830.
USE: In perfumery.

2360. Cladribine. [4291-63-8] 2-Chloro-2'-deoxyadenosine; 2-chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuran-

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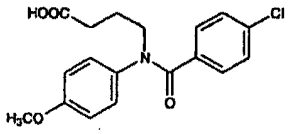
osyl)purine; 2-chlorodeoxyadenosine; 2-CdA; CldAdo; NSC-105014-F; Leustatin. $C_{10}H_{12}ClN_3O_3$; mol wt 285.69. C 42.04%, H 4.23%, Cl 12.41%, N 24.51%, O 16.80%. Substituted purine nucleoside with antileukemic activity. Prepn as intermediate in synthesis of 2-deoxynucleosides: H. Venner, *Ber.* **93**, 140 (1960); M. Ikehara, H. Tada, *J. Am. Chem. Soc.* **85**, 2344 (1963); *eidem, ibid.* **87**, 606 (1965). Synthesis and biological activity: L. F. Christensen *et al., J. Med. Chem.* **15**, 735 (1972). Stereospecific synthesis: Z. Kazimierczuk *et al., J. Am. Chem. Soc.* **106**, 6379 (1984); R. K. Robins, G. R. Revankar, EP 173059; *eidem*, US 4760137 (1986, 1988 both to Brigham Young Univ.). Specific toxicity to lymphocytes: D. A. Carson *et al., Proc. Nat. Acad. Sci. USA* **77**, 6865 (1980); *eidem, Blood* **62**, 737 (1983). Mechanism of action: S. Seto *et al., J. Clin. Invest.* **75**, 377 (1985). Clinical evaluation in chronic lymphocytic leukemia: L. D. Piro *et al., Blood* **72**, 1069 (1988); in hairy cell leukemia: *eidem, N. Engl. J. Med.* **322**, 1117 (1990).



Crystals from water, softens at 210-215°, solidifies and turns brown (Christensen). Also reported as crystals from ethanol, mp 220° (softens), resolidifies, turns brown and does not melt below 300° (Kazimierczuk). $[\alpha]_D^{25}$ −18.8° (c = 1 in DMF). uv max in 0.1*N* NaOH: 265 nm; in 0.1*N* HCl: 265 nm.

THERAP CAT: Antineoplastic.

2361. Clanobutin. [30544-61-7] 4-[(4-Chlorobenzoyl)-(4-methoxyphenyl)amino]butanoic acid; 4-[*p*-chloro-*N*-(*p*-methoxyphenyl)benzamido]butyric acid; *N*-(*p*-chlorobenzoyl)-γ-(*p*-anisidino)butyric acid; Bykahepar. $C_{18}H_{18}ClNO_4$; mol wt 347.80. C 62.16%, H 5.22%, Cl 10.19%, N 4.03%, O 18.40%. Prepn: K. Klemm *et al.*, DE 1917036 corresp to US 3780095 (1971, 1973 both to Byk-Gulden). Series of articles on synthesis, physical and pharmacological properties: *Arzneimittel-Forsch.* **29**, 1-15 (1979). *In vitro* biochemical study: H. Wolf *et al., Biochem. Pharmacol.* **29**, 1649 (1980). Effect on bile excretion in rats, dogs: P. Berchtold *et al., Arzneimittel-Forsch.* **30**, 1878 (1980).

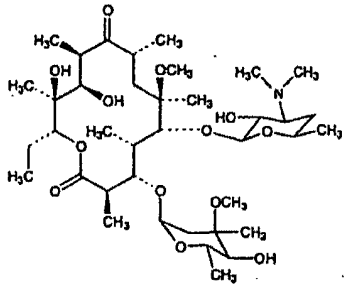


Cryst from ethyl acetate, mp 115-116°. pKa 5.04. Soly in water at 37°: 4.02×10^{-2} mol/l at pH 7. LD_{50} in rats (mg/kg): >2000 orally; 570 i.v. (Klemm).

THERAP CAT: Choleretic.

THERAP CAT (VET): Choleretic; in treatment of piroplasmosis and anaplasmosis.

2362. Clarithromycin. [81103-11-9] 6-*O*-Methylerythromycin; A-56268; TE-031; Biaxin; Clathromycin; Cyllind; Klacid; Klaricid; Macladin; Naxy; Veclam; Zeclar. $C_{38}H_{69}NO_{13}$; mol wt 747.95. C 61.02%, H 9.30%, N 1.87%, O 27.81%. Semisynthetic macrolide antibiotic; derivative of erythromycin, *q.v.* Prepn: Y. Watanabe *et al.*, EP 41355; *eidem*, US 4331803 (1981, 1982 both to Taisho); and *in vitro* antibacterial activity: S. Morimoto *et al., J. Antibiot.* **37**, 187 (1984). *In vitro* and *in vivo* antibacterial activity: P. B. Fernandes *et al., Antimicrob. Ag. Chemother.* **30**, 865 (1986). Comparative antibacterial spectrum *in vitro*: C. Benson *et al., Eur. J. Clin. Microbiol.* **6**, 173 (1987); H. M. Wexler, S. M. Finegold, *ibid.* 492. HPLC determn in biological fluids: D. Croteau *et al., J. Chromatog.* 419, 205 (1987). Acute toxicity study: S. Abe *et al., Chemotherapy (Tokyo)* **36**, Suppl. 3, 274 (1988). Symposium on pharmacology and comparative clinical studies: *J. Antimicrob. Chemother.* **27**, Suppl. A, 1-124 (1991). Comprehensive description: I. I. Salem, *Anal. Profiles Drug Subs. Exctp.*, **24**, 45-85, (1996).



Colorless needles from chloroform + diisopropyl ether (1:2), mp 217-220° (dec). Also reported as crystals from ethanol, mp 222-225° (Morimoto). uv max ($CHCl_3$): 288 nm (ε 27.9). uv max ($CHCl_3$): 240, 288 nm; (methanol): 211, 288 nm. $[\alpha]_D^{25}$ −90.4° (c = 1 in $CHCl_3$). Stable at acidic pH. LD_{50} in male, female mice, male, female rats (mg/kg): 2740, 2700, 3470, 2700 orally, 1030, 850, 669, 753 i.p., >5000 all s.c. (Abe).

THERAP CAT: Antibacterial.

2363. Clathrates. Compounds that are capable of trapping other substances within their own crystal lattices. The cavities of the host molecules are classified as cages, tunnels, or layered types, depending on the way they include guest molecules. The geometry of the cavities limits the guest molecules by size and shape, rather than by chemical similarity with the host molecules. Among common clathrates are *molecular sieves*, *cyclotriphosphazenes*, and *Dianin's compound*, as well as hydroquinone, cyclodextrins, *o*-thymotide, and deoxycholic acid, *q.q.v.* *Cavitands* are organic hosts with enforced (rigid) cavities: D. J. Cram, *Science* **219**, 1177 (1983); R. C. Helgeson *et al., Chem. Commun.* 1983, 101. Comprehensive book: *Clathrate Compounds*, V. M. Bhatnagar, Ed. (Chemical Pub. Co., New York, 1970) 244 pp. *Reviews:* D. D. MacNicol *et al., Chem. Soc. Rev.* **7**, 65-87 (1978); E. C. Makin, "Clathrallon" in *Kirk-Othmer Encyclopedia of Chemical Technology* Vol. 6 (Wiley-Interscience, New York, 3rd ed., 1979) pp 178-189.

USE: As complexing agent; stabilizing agent. In analytical separations.

2364. Clavulanic Acid. [58001-44-8] [2*R*-(2α,3*Z*,5α)]-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid; MM 14151. $C_8H_9NO_5$; mol wt 199.16. C 48.25%, H 4.55%, N 7.03%, O 40.17%. β-Lactamase inhibitor. Antibiotic produced by *Streptomyces clavuligerus;* first reported naturally occurring fused β-lactam containing oxygen. Isoln: M. Cole *et al.*, DE 2517316 (1975 to Beecham), *C.A.* **84**, 72635t (1976); A. G. Brown *et al., J. Antibiot.* **29**, 668 (1976). Structure, x-ray crystallography: T. T. Howarth *et al., Chem. Commun.* 1976, 266. Total synthesis of (±)-form: P. H. Bentley *et al., ibid.* 1977, 748, 905; *eidem, Tetrahedron Letters* 1979, 1889. β-Lactamase inhibition and antibacterial spectrum: C. Reading, M. Cole, *Antimicrob. Ag. Chemother.* **11**, 852 (1977). Mechanism of action: B. G. Spratt *et al., ibid.* **12**, 406 (1977). Antibacterial activity, pharmacology and clinical efficacy of combination with amoxicillin: A. P. Ball *et al., Lancet* **1**, 620 (1980); R. N. Brogden *et al., Drugs* **22**, 337-362 (1981). *In vitro* and *in vivo* synergism with ticarcillin: R. Sutherland *et al., Am. J. Med.* **79**, Suppl. 5B, 13 (1985).

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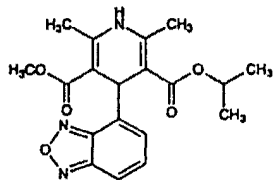
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angina and coronary artery disease: C. E. Handler, E. Sowton, *ibid.* 27, 415 (1984); in hypertension: E. B. Nelson *et al., Clin. Pharmacol. Ther.* 40, 694 (1986). Comparison of hemodynamic effects of enantiomers: R. P. Hof *et al., J. Cardiovasc. Pharmacol.* 8, 221 (1986). Series of articles on pharmacology and clinical use: *Am. J. Med.* 86, 1-146 (1989).



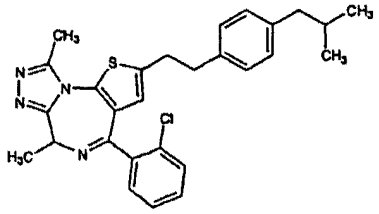
mp 168-170°.

S(+)-Form. PN-205-033. Crystals from ether + hexane, mp 142°. $[\alpha]_D^{20}$ +6.7° (c = 1.5 in ethanol).

R(−)-Form. PN-205-034. Crystals from ether + hexane, mp 140°. $[\alpha]_D^{20}$ −6.7° (c = 1.67 in ethanol).

THERAP CAT: Antihypertensive; antianginal.

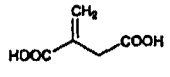
5263. Israpafant. [117279-73-9] 4-(2-Chlorophenyl)-6,9-dimethyl-2-[2-[4-(2-methylpropyl)phenyl]ethyl]-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine; (±)-4-(*o*-chlorophenyl)-2-(*p*-isobutylphenethyl)-6,9-dimethyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine; Y-24180; Pafnol. $C_{28}H_{29}ClN_4S$; mol wt 489.09. C 68.76%, H 5.98%, Cl 7.25%, N 11.46%, S 6.56%. Platelet activating factor (PAF) antagonist. Prepn: T. Tahara *et al.*, EP 268242; *eidem*, US 4820703 (1988, 1989 both to Yoshitomi). Pharmacology: M. Terasawa *et al., Prostaglandins* 40, 553 (1990). Receptor binding study: S. Takehara *et al., ibid.* 571. Clinical evaluation in asthma: S. Hozawa *et al., Am. J. Respir. Crit. Care Med.* 152, 1198 (1995).



Colorless crystals from isopropyl ether, mp 129.5-131.5°. Sol in propylene glycol.

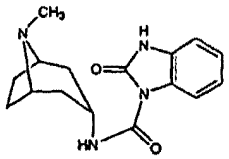
THERAP CAT: Antiasthmatic.

5264. Itaconic Acid. [97-65-4] Methylenesuccinic acid; propylenedicarboxylic acid. $C_5H_6O_4$; mol wt 130.10. C 46.16%, H 4.65%, O 49.19%. Obtained by dry distillation of citric acid and subsequent treatment of the anhydride with water. Produced on a large scale by submerged aerobic fermentation using *Aspergillus terreus* and low cost carbohydrates from beet or cane: Kane *et al.*, US 2385283 (1945 to Pfizer). Synthesis from propargyl chloride, carbon monoxide, nickel carbonyl and water: Chiusoli, US 3025320 (1962 to Montecatini).



Hygroscopic crystals; characteristic odor. d 1.63. mp 162-164° with decompn. Also reported as mp 172° [Kinoshita, *Acta Phytochem. (Japan)* 5, 273 (1931)]. One gram dissolves in 12 ml water, 5 ml alcohol; very slightly sol in benzene, chloroform, ether, carbon disulfide, petr ether. *Keep well closed.*

5265. Itasetron. [123258-84-4] 2,3-Dihydro-*N*-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2-oxo-1*H*-benzimidazole-1-carboxamide; 2-oxo-*N*-1α*H*,5α*H*-tropan-3α-yl-1-benzimidazoline-1-carboxamide. $C_{16}H_{20}N_4O_2$; mol wt 300.35. C 63.98%, H 6.71%, N 18.65%, O 10.65%. Serotonin ($5\text{-}HT_3$) receptor antagonist. Prepn: M. Turconi *et al.*, EP 309423 (1989 to Istituto De Angeli); *eidem*, US 5223511 (1993 to Boehringer, Ing.); M. Turconi *et al., J. Med. Chem.* 33, 2101 (1990). Pharmacology: *idem et al., Eur. J. Pharmacol.* 203, 203 (1991). Mode of action: M. B. Passani *et al., Brit. J. Pharmacol.* 112, 695 (1994). Clinical efficacy and tolerability: H. Goldschmidt *et al., Anti-Cancer Drugs* 8, 436 (1997). Review of therapeutic potential: M. B. Passani, R. Corradetti, *CNS Drug Reviews* 2, 195-213 (1996).

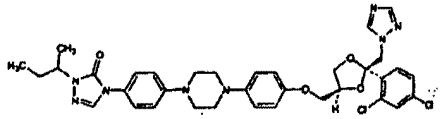


Crystals from acetonitrile, mp 205-207°. LD_{50} in mice, rats (mg/kg): 56, 62 i.v. (Passani).

Hydrochloride. [127618-28-4] DAU 6215. $C_{16}H_{20}N_4O_2 \cdot HCl$; mol wt 336.82. Colorless crystals, mp 270°.

THERAP CAT: Antiemetic.

5266. Itraconazole. [84625-61-6] 4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; (±)-1-*sec*-butyl-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one; oriconazole; R-51211; Itrizole; Sporanox; Triasporin. $C_{35}H_{38}Cl_2N_8O_4$; mol wt 705.65. C 59.57%, H 5.43%, Cl 10.05%, N 15.88%, O 9.07%. Orally active antimycotic structurally related to ketoconazole, *q.v.* Prepn: J. Heeres, L. J. J. Backx, EP 6711; *eidem*, US 4267179 (1980, 1981 both to Janssen); J. Heeres *et al., J. Med. Chem.* 27, 894 (1984). *In vitro* activity: A. Espinel-Ingroff *et al., Antimicrob. Ag. Chemother.* 26, 5 (1984). HPLC determn in biological samples: R. Woestenborghs *et al., J. Chromatog.* 413, 332 (1987). Symposium on pharmacology and clinical efficacy: *Rev. Infect. Dis.* 9, Suppl 1, S1-S152 (1987). Toxicity data: H. Van Cauteren *et al., ibid.* S43. Review of clinical pharmacokinetics: J. Heykants *et al., Mycoses* 32, Suppl 1, 67-87 (1989); of clinical efficacy in dermatophytosis: P. De Doncker, G. Cauwenbergh, *Brit. J. Clin. Pract.* Suppl. 71, 118-122 (1990). *Review:* A. M. Sugar, *Curr. Clin. Topics Inf. Dis.* 13, 74-98 (1993).



Crystals from toluene, mp 166.2°. pKa 3.7. Lipophilic; partition coefficient (*n*-octanol/aq buffer of pH 8.1): 5.66. Practically insol in water and dil acidic solns. LD_{50} (14 day) in mice, rats, dogs (mg/kg): >320, >320, >200 orally (Van Cauteren).

THERAP CAT: Antifungal.

5267. Itramin Tosylate. [13445-63-1] 2-Aminoethanol nitrate mono(4-methylbenzenesulfonate); 2-aminoethanol nitrate mono-*p*-toluenesulfonate; 2-nitratoethylaminotoluene-*p*-sulfonate; Cardisan; Tostram; Nilatil. $C_9H_{14}N_2O_6S$; mol wt 278.28. C 38.85%, H 5.07%, N 10.07%, O 34.50%, S 11.52%. Prepn: SE 168308 (1959 to Aktiebolaget Pharmacia), *CA* 54, 24405d (1960).

Hydroxypropyl-beta-cyclodextrin
CAS No:94035-02-6

Name: Hydroxypropyl-beta-cyclodextrin

Synonyms: beta-Hydroxypropylcyclodextrin
beta-Cyclodextrin, 2-hydroxypropyl ether
HPB
2-Hydroxypropyl-beta-cyclodextrin
128446-35-5

CAS Number: 94035-02-6

Molecular Formula: $C_{42}(H)_{70-n}O_{35}(C_3H_7)_n$

Melting Point: 278 °C

Safety Description: S24/25 Details

	List of Suppliers for **Hydroxypropyl-beta-cyclodextrin**	Country
☐ inquire now		
☐	Onbio Inc. Introduction:HYDROXYPROPYL-BETA-CYCLODEXTRIN	United St
☐	Yiming Fine Chemicals Co., Ltd. Introduction:mp : 267 °C (dec.) storage temp. : 2-8°C solubility : H2O. 45 % (w/v) form : solution (clear, colorless)	China (Mair

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Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

Name	Description	Size	Catalog #	Supplier	
CKBB	Recombinant Human Creatine Kinase BB Isoenzyme	10µg, 50µg, 1mg	CKI- 268	PROSPEC-TANY TECHNOGENE LTD.	More In
Ckdk6	The RP-39008 Ckdk6 protein is a partial length (aa 1-327) bacterially expressed recombinant protein.RP-39008 is suitable for use as a control in ELISA and Western blot applications.The RP-39008 protein is GST-tagged.	10 ug	RP-39008	ABR - AFFINITY BIOREAGENTS INC.	More In
CKMM	Human Creatine Kinase MM	200µg, 1mg, 10mg	CKI- 273	PROSPEC-TANY TECHNOGENE LTD.	More In
CKS-17	Sequence: Leu-Gln-Asn-Arg-Arg-Gly-L eu-Asp-Leu-Leu-Phe-Leu-Ly s-Glu-Gly-Gly-LeuStorage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. R...	1mg	C5818-05	UNITED STATES BIOLOGICAL	More In
CKS-17 (7-12)	Sequence: Leu-Asp-Leu-Leu-Phe-LeuSt orage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. Reconstituted product is stable for 12 months...	25mg	C5818-05A	UNITED STATES BIOLOGICAL	More In

CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	0.5 mg	06-271-83162	GENWAY BIOTECH INC.	More In
CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	1 mg	06-271-83162	GENWAY BIOTECH INC.	More In
CARCINOEMBRYONIC ANTIGEN (CL)	testing/assay service	n/a	n/a	RDL REFERENCE LABORATORY INC.	More In
CASPASE-3/7 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	More In
CASPASE-8 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	More In
CASPASE-9 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	More In
CASPASE (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	More In
CL 218872	Benzodiazepine agonist displaying selectivity for α1 subunit-containing GABAA receptors (Ki values are 130, 1820, 1530, > 10000, 490 and > 10000 nM for α1, α2, α3, α4, α5 and α6-subunit containing re...	10mg, 50mg	1709	TOCRIS BIOSCIENCE	More In
CL-387,785	Irreversibly inhibits EGF-receptor (EGFR) kinase activity in vivo (IC50 = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR in vivo (IC50 = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits prolifer...	n/a	233100	CALBIOCHEM/EMD BIOSCIENCES	More In
	A selective inhibitor of MMP-13 (IC50 = 10 μM).				

CL-82198	Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	n/a	233105	CALBIOCHEM/EMD BIOSCIENCES	More In
Calphostin C, Cladosporium cladosporioides	A cell permeable, highly specific inhibitor of protein kinase C (IC50 = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca2+ or phospholi...	n/a	208725	CALBIOCHEM/EMD BIOSCIENCES	More In
Cladribine	It is a substituted purine nucleoside with antileukemic activity.Melting Point: 220-235?C dec.Solubility: Methanol, Water	50mg	C5819-75	UNITED STATES BIOLOGICAL	More In
Clarithromycin	A semi-synthetic macrolide antibiotic. A derivative of erythromycin.Melting Point: 217-220?C dec.Solubility: Chloroform, Ethanol	50mg	C5829	UNITED STATES BIOLOGICAL	More In
Clavulanic Acid	A B-Lactamase inhibitor.	10mg	C5836	UNITED STATES BIOLOGICAL	More In
CLIC3	The RP-39009 CLIC3 protein is a full length bacterially expressed recombinant protein.RP-39009 is suitable for use as a control in ELISA and Western blot applications.The RP-39009 amino acid sequence corresponds to the NCBI accession number NP_004...	10 ug	RP-39009	ABR - AFFINITY BIOREAGENTS INC.	More In
Clidinium Bromide	An anticholinergic. Used as an antispasmodic.Melting Point: 240-241?C	5g	C5840-75	UNITED STATES BIOLOGICAL	More In
	A metal ion chelator that crosses the blood brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve				

Clioquinol	senile plaques and reduce amyloid's ability to clump together, apparently by trapping the Cu2+ and Zn2+ that stud these depos...	n/a	233165	CALBIOCHEM/EMD BIOSCIENCES	More In
CLK3, active	n/a	10 ug	14-724	MILLIPORE	More In
CLK2, active	n/a	10 ug	14-774	MILLIPORE	More In
Clofarabine	ISecond generation purine nucleoside analog; antimetabolite that inhibits DNA synthesis and resists deamination by adenosine deaminase. Antineoplastic.Melting Point: 225-227?C	10mg	C5843-55	UNITED STATES BIOLOGICAL	More In
Clofarabine	Deoxycytidine kinase (dCK) substrate. Phosphorylated to form clofarabine triphosphate, which competes with dATP for DNA polymerase- α and - ε and potently inhibits ribonucleotide reductase (IC50 = 65 nM). Induces apoptosis by directl...	10mg, 50mg	2600	TOCRIS BIOSCIENCE	More In
CLOFIBRATE	n/a	n/a	n/a	CAYMAN CHEMICAL CO.	More In
Clofibrate	PPAR agonist (EC50 values are 50, 500 and > 100 µM at PPAR α, PPAR γ and PPAR δ respectively). Antihyperlipoproteinemic.	1g	0824	TOCRIS BIOSCIENCE	More In
Clofibric acid	PPAR agonist. Antihyperlipoproteinemic.	1g	0825	TOCRIS BIOSCIENCE	More In
Clofibrate	An anti-hyperlipoproteinemic agent believed to act by inhibiting cholesterol biosynthesis. Activates PPARα and induces cytochrome P450 4A1 and 4A3. Imparts protection against acetaminophen toxicity and increases hepatic glutathione levels.	n/a	231405	CALBIOCHEM/EMD BIOSCIENCES	More In
Clofulbicyne	n/a	1 mg.	TXL9001-1	ACCURATE CHEMICAL & SCIENTIFIC CO.	More In

Clofulbicyne	n/a	5x1 mg.	TXL9001-5	ACCURATE CHEMICAL & SCIENTIFIC CO.	More In
Clomifene citrate	International Chemical Reference Substances are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in t...	100 mg	9930259	W.H.O. COLLABORATING CENTRE	More In
Clomiphene, Citrate	An unducer of ovulation. A gonad-stimulating principle.Melting Point: 116.5-118?CSolubility: Methanol	10g	C5843-65	UNITED STATES BIOLOGICAL	More In
Cloning	>1500 bp into 3 different expression vectors	n/a	PE05-0003	HYPEROMICS FARMA INC.	More In
Cloning	<1500 bp into 3 different expression vectors	n/a	PE05-0002	HYPEROMICS FARMA INC.	More In
Clopidogrel Carboxylic Acid	A metabolite of the drug Clopidogrel.Solubility: Methanol, Water	5mg	C5849-01	UNITED STATES BIOLOGICAL	More In
CLOSTRIPAIN Clostridium	n/a	n/a	n/a	PROMEGA CORPORATION	More In
Clotrimazole	An antifungal agent that acts as a potent and specific inhibitor of the Ca2+-activated K+ channel (Gardos channel; IC50 = 650 nM). Prevents K+ loss and dehydration of sickled erythrocytes.	n/a	233230	CALBIOCHEM/EMD BIOSCIENCES	More In
Clozapine	An antipsychotic.Melting Point: 183-184? CSolubility: Acetone, Ether	250mg	C5866	UNITED STATES BIOLOGICAL	More In
Clozapine	Atypical antipsychotic drug, with a much lower tendency to cause extrapyramidal side effects than conventional neuroleptics. Displays a broad range of pharmacological actions; the antipsychotic effects are thought to be mediated principally by 5-H...	50mg, 500mg	0444	TOCRIS BIOSCIENCE	More In

CLTB	The RP-39010 CLTB protein is a full length bacterially expressed recombinant protein.RP-39010 is suitable for use as a control in ELISA and Western blot applications.The RP-39010 amino acid sequence corresponds to the NCBI accession number NP_0018...	10 ug	RP-39010	ABR - AFFINITY BIOREAGENTS INC.	More In
Aldosterone-3 CMO (BSA)	The major mineralcorticoid, which is secreted almost independently of ACTH from the pitutitary, is aldosterone. Aldosterone secretion is controlled mostly by the levels of potassium and sodium in serum and a blood pressure control system called th...	5mg	A1350-04	UNITED STATES BIOLOGICAL	More In
Androstenedione-3 (CMO)	Androstenedione was discovered in 1935. It is naturally produced in men and women. It is a direct precursor to the hormone testosterone. The liver converts androstenedione to testosterone.Precursor:4-Androsten-3,17-dione-3Sto rage and Stability:Lyo...	10mg	A2292-02	UNITED STATES BIOLOGICAL	More In
CMPD-1	Non-ATP-competitive, selective inhibitor of p38 α-mediated MK2a (mitogen-activated protein kinase-activated protein kinase 2a) phosphorylation (apparent Ki = 330 nM). Does not inhibit p38 α-mediated phosphorylation of the two other kno...	10mg, 50mg	2186	TOCRIS BIOSCIENCE	More In
CMV	Glycine Extract	mL	0810003GE	ZEPTOMETRIX CORP.	More In
CMV	Cytomegalovirus (AD169) Infected Cell Extract. Used for IgG assays - Control is NHDF AV043	n/a	CV001	EASTCOAST BIO INC.	More In
	Cytomegalovirus				

CMV	Gradient Purified. Used for IgM assays.	n/a	CV046	EASTCOAST BIO INC.	More In
CMV	Cytomegalovirus Ag slides for FA. Made to Order	n/a	CG015	EASTCOAST BIO INC.	More In
CMV	Part Pure	n/a	J43010	BIOSPACIFIC INC.	More In

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

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	Examiner Jonathan S. Lau	Art Unit 1623	AIA (First Inventor to File) Status No

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- 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 *28 May 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1-61 and 65-88* is/are pending in the application.

5a) Of the above claim(s) *9-24,32-45 and 65-88* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8,25-31 and 46-61* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ The drawing(s) filed on _____ 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).

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).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 28 May 2013, in which claims 62-64 are canceled and new claims 65-88 are added.

This application is a domestic application, filed 7 Jan 2011; and claims benefit as a CON of 10/551,205, issued as Patent 7,888,328, which is a 371 of PCT/US2004/009387, filed 26 Mar 2004, which claims benefit of provisional application 60/458,922, filed 28 Mar 2003, and claims benefit of provisional application 60/484,756, filed 2 Jul 2003, and claims benefit of provisional application 60/541,247, filed 4 Feb 2004. The filing date of the instant claims is deemed to be provisional application 60/541,247, filed 4 Feb 2004.

Claims 1-61 and 65-88 are pending in the current application. Claims 9-24, 32-45 and new claims 65-88, drawn to non-elected inventions, are withdrawn. Claims 1-8, 25-31 and 46-61 are examined on the merits herein.

Election/Restrictions

Newly submitted claims 65-88 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: New claims 65-88

are encompassed within the invention of Group II detailed in the Restriction Requirement mailed 8 Nov 2012, drawn to a method of treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to a subject in need thereof a pharmaceutical composition comprising said cladribine-cyclodextrin complex.

New Claims 65-88 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 8 Jan 2013.

Regarding Applicant's remarks filed 28 May 2013, if the method of use of claims 65-88 require all limitations of an allowable product then they will be rejoined for examination on the merits. New claims 65-88 are encompassed within the invention of Group II detailed in the Restriction Requirement mailed 8 Nov 2012, and will be considered for rejoinder upon finding allowable claims.

Rejections Withdrawn

Applicant's Amendment, filed 28 May 2013, with respect that claims 1-8, 25-31 and 46-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, provided by Applicant in IDS mailed 7 Jan 2011) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record) has been fully considered and is persuasive, as Applicant provides

evidence in Van Axel Castelli comparing the physical mixture of cladribine-CD prepared by physical mixture and kneading (Van Axel Castelli, page 3898, left column, paragraph 3) with the complex of the instant invention. In view of newly discovered reference to Redenti et al. (Int. J. Pharm., 1996, 129, p289-294, cited in PTO-892), Applicant's remarks are persuasive that the mixture taught by Schultz in view of Baert can reasonably be concluded to be the physical mixture, and the comparative evidence provided by Van Axel Castelli is applicable and persuasive.

This rejection has been **withdrawn**. However, upon further consideration, a new ground(s) of rejection is made in view of Vandercruys (US Patent Application Publication 2002/0150616, published 17 Oct 2002, filed 27 May 1998, cited in PTO-892).

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-8, 25-31 and 46-61 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Vandercruys (US Patent Application Publication 2002/0150616, published 17 Oct 2002, filed 27 May 1998, cited in PTO-892) in view of Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, provided by Applicant in IDS mailed 7 Jan 2011), Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record), Redenti et al. (Int. J. Pharm., 1996, 129, p289-294, cited in PTO-892), and Pitha et al. (Life Sci., 1998, 43, p493-502, cited in PTO-892).

Vandercruys teaches pharmaceutical composition comprising a cyclodextrin and a sparingly water-soluble drug (abstract). Vandercruys teaches the components are preferably in the glass thermoplastic phase without a crystalline or microcrystalline phase (paragraph 13 spanning pages 1-2), or an amorphous phase. Vandercruys teaches the cyclodextrin can be 2-hydroxypropyl-gamma-CD, and in particular 2-hydroxypropyl-beta-CD (page 2, paragraph 20-21). Vandercruys teaches the cyclodextrin includes sulfobutylcyclodextrins (page 2, paragraph 24). Vandercruys teaches varying the molar ratio of cyclodextrin to drug in the range of 100:1 to 5:1, especially 50:1 to 1:2, more especially 10:1 to 1:1 (page 3, paragraph 27). Vandercruys teaches an extensive list of possible drugs which includes cladribine (paragraph 70 spanning pages 4-5). Vandercruys teaches the composition to be an intimate admixture

prepared by dissolving the mixture and removing the solvent (page 6, paragraph 77). Vandercruys implies the mixture results in complexing of the drug in the CD (page 7, paragraphs 87-88). Vandercruys teaches the complex prepared by a vacuum-distillation process (page 8, paragraph 104-105). Vandercruys teaches the pharmaceutical composition in a dosage form for oral administration (page 7, paragraph 95).

Vandercruys does not specifically disclose the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and the composition comprising no significant amount of free crystalline cladribine therein (instant claim 1). Vandercruys does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 7).

Vandercruys does not specifically disclose the complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 25). Vandercruys does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 5 and 29). Vandercruys does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by

weight of the cladribine is in the non-inclusion complex (b) (instant claims 8 and 31). Vandercruys does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, implying a cladribine to cyclodextrin ratio of 1:14.38, or the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 55), implying a cladribine to cyclodextrin ratio of 1:10.55.

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). The disclosed product is substantially identical to the product-by-process. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24). The phrase “one or more cyclodextrin hydroxy groups” combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of “randomly methylated β-cyclodextrins”. Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of the instant claims invention. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg

to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex.

Therefore a composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a "saturated" complex. Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Schultz et al. suggests an amorphous cladribine-cyclodextrin complex in a solid oral dosage form. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the

limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of “about” as a variance of 20% provided in the instant specification page 9, lines 6-11. Such a saturated complex would consist of only (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and being a saturated complex corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

Redenti et al. teaches the one of ordinary skill in the art recognizes the differences between a piroxicam:CD complex prepared by melt-spinning and freeze-drying amorphous piroxicam:CD complex to show that the freeze-dried complex is a true inclusion complex and not a dispersed mixture of two amorphous components (abstract). Redenti et al. suggests the piroxicam:CD complex prepared by melt-spinning is a physical mixture of amorphous piroxicam and amorphous CD, which is subject to recrystallization upon standing (page 290, paragraph spanning left and right column). Redenti et al. teaches the freeze-dried complex does not recrystallize upon standing (page 291, left column, paragraph 2).

Pitha et al. teaches the level of skill in the art regarding the formulation of 2-hydroxypropyl CD to form amorphous mixtures through formation of inclusion complexes (page 493, abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Vandercruys in view of Schultz et al., Baert et al., Redenti et al., and Pitha et al. in order to select the pharmaceutical composition comprising a complex of cyclodextrin and a sparingly water-soluble drug taught by Vandercruys to be a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin and to optimize the ratio of cyclodextrin to the drug. One of ordinary skill in the art would have been motivated to combine Vandercruys in view of Schultz et al., Baert et al., Redenti et al., and Pitha et al. to select a complex of cyclodextrin and cladribine with a reasonable expectation of success because Vandercruys teaches the list of sparingly water-soluble drug includes cladribine and Schultz et al. and Baert et al. provide guidance for selecting the pharmaceutical composition comprising a cyclodextrin and cladribine. One of ordinary skill in the art would have been motivated to make an amorphous complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex and the composition comprising no significant amount of free crystalline cladribine therein because Vandercruys teaches the components are preferably in the glass thermoplastic phase without a crystalline or microcrystalline phase and teaches preparation by dissolving the mixture and removing the solvent by a vacuum-distillation process and implies the mixture results in complexing of the drug in the CD, Redenti et al. suggests a piroxicam:CD complex prepared by melt-spinning is a physical mixture of amorphous piroxicam and amorphous CD, which is subject to recrystallization upon standing while

a freeze-dried complex does not recrystallize upon standing, and Pitha et al. teaches it is known in the art that 2-hydroxypropyl CD forms amorphous mixtures through formation of inclusion complexes, suggesting of the dissolved and vacuum-distilled product of Vandercruys be a complex that does not recrystallize upon standing with a reasonable expectation of success.

It would have been routine experimentation to optimize the ratio of cladribine to cyclodextrin within prior art conditions because Vandercruys teaches varying the molar ratio of cyclodextrin to drug in the range of 100:1 to 5:1, especially 50:1 to 1:2, more especially 10:1 to 1:1 and Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight. See also MPEP 2144.05 II.A, providing "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Claims 46-61 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re

Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed.

The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113. In the instant case, Vandercruys teaches the components are preferably in the glass thermoplastic phase without a crystalline or microcrystalline phase (paragraph 13 spanning pages 1-2) and Vandercruys implies the mixture results in complexing of the drug in the CD (page 7, paragraphs 87-88). Therefore the product in the product-by-process claim is obvious from the product taught by Vandercruys in view of Schultz et al., Baert et al., Redenti et al., and Pitha et al. even though the prior product was made by a different process of Vandercruys teaching the composition to be an intimate admixture prepared by dissolving the mixture and removing the solvent by a vacuum-distillation process.

Response to Applicant's Remarks:

Applicant's Remarks, filed 28 May 2013, have been fully considered and not found to be persuasive regarding the new grounds of rejection.

Applicant's remarks are persuasive regarding rejection over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, provided by Applicant in IDS mailed 7 Jan 2011) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record). Applicant argues that Schultz et al. is non-operable because the process of Baert et al. will result in decomposition of cladribine. However, Schultz et al. in claim 13 and 14 at column 8, lines 40-60 explicitly claims the composition prepared by melt-extrusion. A patent shall be presumed valid and each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. See 35 USC 282. However Redenti et al. (Int. J. Pharm., 1996, 129, p289-294, cited in PTO-892) provides evidence supporting Applicant's remarks that the composition prepared by melt-extrusion is a physical mixture and not a complex.

Applicant's remarks are moot in view of Vandercruys teaching the composition to be an intimate admixture prepared by dissolving the mixture and removing the solvent by a vacuum-distillation process and implying the intimate admixture to be a complex. Vandercruys teaches the components are preferably in the glass thermoplastic phase without a crystalline or microcrystalline phase, or an amorphous complex, and Pitha et al. teaches it is known to one of ordinary skill in the art to use 2-hydroxypropyl CD to form amorphous mixtures through formation of inclusion complexes. Therefore the new grounds of rejection over Vandercruys in view of Schultz et al., Baert et al., Redenti et al., and Pitha et al. teaches all structural limitations of the product and product-by-process as instantly claimed.

The following grounds of rejection are maintained.

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, 25-31 and 46-61 are rejected on the ground of nonstatutory double patenting over claims 1-28 of U. S. Patent No. 7,888,328 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: claims 1-28 of U. S. Patent No. 7,888,328 recite a narrower genus of cladribine-cyclodextrin complex and composition comprising thereof wherein said cyclodextrin is hydroxypropyl-β-cyclodextrin and the weight ratio of from about 1:10 to about 1:16. Claims 12-28 of U. S. Patent No. 7,888,328 recite a product-by-process encompassed within the product-by-process of instant claims 46-61. Therefore claims 1-28 of U. S. Patent No. 7,888,328 supports an anticipation-type nonstatutory double patenting rejection over instant claims 1-8, 25-31 and 46-61.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Response to Applicant's Remarks:

Applicant's Remarks, filed 28 May 2013, have been fully considered and not found to be persuasive.

Applicant notes that the distinction between 1) "same invention" type double patenting statutorily based on 35 USC 101 and 2) nonstatutory-type double patenting rejection, commonly called an "obviousness-type double patenting rejection". To clarify the language of the above rejection, it is meant that anticipation is the epitome of obviousness in the context of patent examination, therefore the above rejection which is stated to be "on the ground of nonstatutory double patenting" (emphasis added) in the rejection statement is performed with an anticipation-type analysis which is meant to be the epitome of obviousness. Applicant is correct that the nonstatutory-type double patenting rejection detailed herein falls within the 2nd category and would be overcome by filing of a terminal disclaimer. Applicant's remarks state that a terminal disclaimer was filed, however a review of the record of the instant application shows no terminal disclaimer has been filed. Clarification is requested regarding the terminal disclaimer.

This rejection is maintained because the record shows no terminal disclaimer has been filed.

Conclusion

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Accordingly, this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is (571)270-

3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1623

/Jonathan S Lau/
Examiner, Art Unit 1623

Notice of References Cited	Application/Control No. 12/986,310	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2002/0150616	10-2002	VANDECRUYS, ROGER PETRUS GEREBERN	424/464
	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	Redenti et al., Int. J. Pharm., 1996, 129, p289-294.
	V	Pitha et al., Life Sci., 1998, 43, p493-502.
	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
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor, Yogesh Dandiker)	2/15/2013	JSL
EAST - see attached notes	2/15/2013	JSL
Google Scholar - see attached notes	2/15/2013	JSL
Google Scholar - see attached notes	9/3/2013	JSL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012	02/15/2013	09/03/2013						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	✓	✓						
	4	÷	✓	✓						
	5	÷	✓	✓						
	6	÷	✓	✓						
	7	÷	✓	✓						
	8	÷	✓	✓						
	9	÷	N	N						
	10	÷	N	N						
	11	÷	N	N						
	12	÷	N	N						
	13	÷	N	N						
	14	÷	N	N						
	15	÷	N	N						
	16	÷	N	N						
	17	÷	N	N						
	18	÷	N	N						
	19	÷	N	N						
	20	÷	N	N						
	21	÷	N	N						
	22	÷	N	N						
	23	÷	N	N						
	24	÷	N	N						
	25	÷	✓	✓						
	26	÷	✓	✓						
	27	÷	✓	✓						
	28	÷	✓	✓						
	29	÷	✓	✓						
	30	÷	✓	✓						
	31	÷	✓	✓						
	32	÷	N	N						
	33	÷	N	N						
	34	÷	N	N						
	35	÷	N	N						
	36	÷	N	N						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012	02/15/2013	09/03/2013						
	37	÷	N	N						
	38	÷	N	N						
	39	÷	N	N						
	40	÷	N	N						
	41	÷	N	N						
	42	÷	N	N						
	43	÷	N	N						
	44	÷	N	N						
	45	÷	N	N						
	46	÷	✓	✓						
	47	÷	✓	✓						
	48	÷	✓	✓						
	49	÷	✓	✓						
	50	÷	✓	✓						
	51	÷	✓	✓						
	52	÷	✓	✓						
	53	÷	✓	✓						
	54	÷	✓	✓						
	55	÷	✓	✓						
	56	÷	✓	✓						
	57	÷	✓	✓						
	58	÷	✓	✓						
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	60	÷	✓	✓						
	61	÷	✓	✓						
	62	÷	N	-						
	63	÷	N	-						
	64	÷	N	-						
	65			N						
	66			N						
	67			N						
	68			N						
	69			N						
	70			N						
	71			N						
	72			N						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	10/18/2012	02/15/2013	09/03/2013						
	73			N						
	74			N						
	75			N						
	76			N						
	77			N						
	78			N						
	79			N						
	80			N						
	81			N						
	82			N						
	83			N						
	84			N						
	85			N						
	86			N						
	87			N						
	88			N						

Google amorphous cyclodextrin

Scholar About 28,500 results (0.03 sec)

Drug solubilizers to aid pharmacologists: **amorphous cyclodextrin** derivatives
J Pitha, T Irie, PB Sklar, JS Nye - Life sciences, 1988 - Elsevier
Abstract Conversion of crystalline α-, β-, or γ-**cyclodextrins** into **amorphous** mixtures of water soluble derivatives yields non-toxic solubilizers which dissolve drugs through the formation of inclusion complexes. From these types of compounds 2-hydroxypropyl ethers of ...
Cited by 213 Related articles All 3 versions Cite

A non-surfactant formulation for alfaxalone based on an **amorphous cyclodextrin**: Activity studies in rats and dogs
KS Estes, ME Brewster, AI Webb, N Bodor - International journal of ..., 1990 - Elsevier
Abstract The steroid anesthetic, alfaxalone, is commercially available for veterinary use in a formulation containing Cremophor-EL® and alfadalone acetate. The allergic sensitivity of some species to this formulation limits its veterinary application and also led to withdrawal ...
Cited by 28 Related articles All 3 versions Cite

Assessment of solid-state interactions of naproxen with **amorphous cyclodextrin** derivatives by DSC
GP Bettinetti, M Sorrenti, S Rossi, F Ferrari... - ... of pharmaceutical and ..., 2002 - Elsevier
A microcalorimetric method based on differential scanning calorimetry (DSC) of drug-additive binary systems to assess kneading-induced interactions was applied to naproxen (NAP) in combinations with **amorphous** hydroxypropyl β-**cyclodextrin** (HPβCd), β- ...
Cited by 11 Related articles All 5 versions Cite

Amorphous water soluble derivatives of **cyclodextrins**: Nontoxic dissolution enhancing excipients
J Pitha, J Pitha - Journal of pharmaceutical sciences, 1985 - Wiley Online Library
Abstract Dissolution properties of drugs may be improved by their conversion to an **amorphous** state or by complexation with **cyclodextrins**. The present report describes the preparation of **cyclodextrin** derivatives which are intrinsically **amorphous**, and water- ...
Cited by 184 Related articles All 4 versions Cite

Carbon-13 CP/MAS NMR studies of amylose inclusion complexes, **cyclodextrins**, and the **amorphous** phase of starch granules: relationships between glycosidic ...
MJ Gidley, SM Bociek - Journal of the American Chemical Society, 1988 - ACS Publications
Abstract: In order to characterize molecular conformations within starch granules and to examine the relationships between polysaccharide conformation and solid state 13C chemical shifts, a range of polymeric and oligomeric a-(1-4) glucans has been examined ...
Cited by 251 Related articles All 4 versions Cite

Use of 2-hydroxypropyl-β-**cyclodextrin** as a solubilizing and stabilizing excipient for protein drugs
ME Brewster, MS Hora, JW Simpkins, N Bodor - Pharmaceutical research, 1991 - Springer
... T. Irie, K. Fukanaga, A. Yoshida, K. Uekama, H. Fales, and J. Pitha. **Amorphous** water-soluble **cyclodextrin** derivatives. Pharm. Res. 5:713-717 (1988). J. Pitha and J. Pitha. **Amorphous**

water-soluble derivatives of **cyclodextrins**: Nontoxic dissolution enhancing excipients. ...
Cited by 125 Related articles All 6 versions Cite

An intravenous toxicity study of 2-hydroxypropyl-β-**cyclodextrin**, a useful drug solubilizer, in rats and monkeys [PDF] from addlandcassi.com

ME Brewster, KS Estes, N Bodor - International journal of pharmaceutics, 1990 - Elsevier

... Pharmaceutical preparations containing **cyclodextrin** derivatives. (1988) US Patent 4, 727, 064. Pitha and Pitha, 1985; J. Pitha, J. Pitha; **Amorphous** water-soluble derivatives of **cyclodextrins**: nontoxic dissolution enhancing excipients. J. Pharm. Sci., 74 (1985), pp. 987–990. ...
Cited by 92 Related articles All 6 versions Cite

Characterization of physicochemical properties of naproxen systems with **amorphous** β-**cyclodextrin**-epichlorohydrin polymers

P Mura, MT Faucci, F Maestrelli, S Furlanetto... - ... of pharmaceutical and ..., 2002 - Elsevier

Ground mixtures of naproxen with **amorphous** β-**cyclodextrin**-epichlorohydrin soluble (βCd-EPS) or insoluble cross-linked (βCd-EPI) polymers were investigated for both solid phase characterization (Differential Scanning Calorimetry, powder X-ray Diffractometry) and ...
Cited by 52 Related articles All 5 versions Cite

Evaluation of the cytotoxicity of **cyclodextrins** and hydroxypropylated derivatives

F Leroy-Lechat, D Wouessidjewe, JP Andreux... - International journal of ..., 1994 - Elsevier

... 373–376. Pitha et al., 1988; J. Pitha, T. Irie, PB Sklar, JS Nye; Drug solubilizers to aid pharmacologists. **Amorphous cyclodextrin** derivatives. Life Sci., 43 (1988), pp. 493–502. ... Pitha, 1990; J. Pitha; Hydroxypropyl **cyclodextrins** in pharmacy and pharmacology, Progress from toy ...
Cited by 57 Related articles All 2 versions Cite

A study on the differentiation between **amorphous** piroxicam: β-**cyclodextrin** complex and a mixture of the two **amorphous** components

E Redenti, T Peveri, M Zanol, P Ventura... - International journal of ..., 1996 - Elsevier

Amorphous piroxicam was prepared by the melt spinning method to prove that freeze-dried **amorphous** piroxicam: β-**cyclodextrin** is a true inclusion compound and not a dispersed mixture of the two **amorphous** components. Differential scanning calorimetry (DSC) and ...
Cited by 42 Related articles All 3 versions Cite

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Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	12986310
Filing Date	07-Jan-2011
First Named Inventor	Nicholas Bodor
Attorney Docket Number	20009904-0067
Title of Invention	ORAL FORMULATIONS OF CLADRIBINE

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
ARES TRADING S.A.	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

7888328

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted 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.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 26254 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors ○ A joint inventor; all of whom are signing this request ○ The assignee of record of the entire interest that has properly made itself of record pursuant to 37 CFR 3.71

Signature	/Mary Katherine Baumeister/
Name	Mary Katherine Baumeister

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	12986310
Filing Date:	07-Jan-2011
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Attorney Docket Number:	20009904-0067

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Statutory or Terminal Disclaimer	1814	1	160	160
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($)
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 12986310

Filing Date: 07-Jan-2011

Applicant/Patent under Reexamination: Bodor et al.

Electronic Terminal Disclaimer filed on December 10, 2013

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	17619390
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	10-DEC-2013
Filing Date:	07-JAN-2011
Time Stamp:	17:12:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	3863
Deposit Account	193140
Authorized User	BAUMEISTER, MARY KATHERINE

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

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	33653 cd7ebb7fc7ab2d741da36316c7177d309545f238	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30094 7fba649f674a214c8b1650534d5c52693ff0f510	no	2
Warnings:					
Information:					
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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.

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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: Nicholas S. BODOR et al.	)	**MAIL STOP AMENDMENT**
	)	
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
	)	
Filed: January 7, 2011	)	Group Art Unit: 1623
	)	
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100
	)	

REPLY TO OFFICIAL ACTION

In response to the Office Action dated September 11, 2013, Applicants submit the remarks below:

REMARKS

Further examination and consideration of the subject application, as pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks that follow.

DOMESTIC PRIORITY

The Examiner's acknowledgment of the several claims for domestic priority is noted, with appreciation.

STATUS OF CLAIMS

Claims 1-61 and 65-88 are now in this application. Claims 9-24, 32-45, and 65-88 have been withdrawn. Claims 1-8, 25-31 and 46-61 are under examination. No amendments have been made.

DISCUSSION OF RESTRICTION REQUIREMENT

Newly submitted Claims 65-88 have been withdrawn from consideration. Applicants appreciate the Examiner's statement that these claims will be considered for rejoinder upon finding allowable claims.

CLAIM REJECTIONS- 35 U.S.C. § 103

Claims 1-8, 25-31 and 46-61 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Vandercruys (U.S. Publication No. 2002/0150616) in view of Schultz et al., (US Patent No. 6,194,395), Baert (International Publication No.

WO97/18839), Redenti et al., (Int. J. Pharm., 1996, 129, p289-294) and Pitha et al., (Life Sci., 1998, 43, p493-502). It is submitted that this rejection cannot be maintained against any of the claims in this application.

The teaching of Vandercruys (US 2002/0150616) is limited to compositions, wherein the drug compound, an acid, a cyclodextrin and an organic polymer are intimately admixed [0011]. Such limitation is also stated in the abstract. As set forth in the present application as filed at page 1, line 15, cladribine is an acid-labile drug. In view of this and the clear teaching that Vandercruys deals with formulations which mandatorily contain an acid ingredient which is detrimental to the stability of cladribine, a person skilled in the art would not have considered Vandercruys if he wanted to develop a formulation for cladribine, despite its mention in a "laundry list" of active ingredients.

All components being present in the composition taught by Vandercruys, i.e. the acid, drug compound, cyclodextrin and organic polymer, are mixed together, whereby it is emphasized that all four components are present and indeed that "mixtures where individual particles do not contain all four components are not preferred". Such intimate admixture is taught as complimentary at the microscopic level [0012] and it is further taught that all components are dispersed to form the chemically and physically uniform homogeneous material throughout which is called a glass thermoplastic phase or system [0013]. Such system is exemplified in Example 1 and is made by solvation of drug compound and acid in the solvent, addition and dissolution of the cyclodextrin and polymer and subsequent evaporation of the solvent. Therefore, Vandercruys provides a clear teaching to combine the drug, an acid, a cyclodextrin and an organic polymer into

one physically and chemically homogeneous thermoplastic system composition preparation.

Vandercruys does not teach a combination of the drug and a cyclodextrin without an acid and an organic polymer. In Example 1, the acid is even present in a severalfold amount of the drug (weight ratio drug : acid = 1 : 5) and in a double amount compared to the cyclodextrin. Example 2 discloses similar weight ratios. It is impermissible to directly deduce a teaching given for a composition containing all components to a part of it consisting of only two components (drug and cyclodextrin). This is especially the case if another ingredient (here an acid) is mandatory and is present in an amount exceeding that which is picked out of it (here cyclodextrin).

The foregoing is even true for the result achieved by a process which is described to be used for the preparation of the composition, i.e. the vacuum distillation process described in the Examples 1 and 2 on page 8.

Further, Vandercruys teaches that the cyclodextrin is preferably present at 5 to 70% by weight relative to the total weight of cyclodextrin, acid, organic polymer and drug, and that the molar ratio of cyclodextrin to drug preferably lies in the range of 100 :1 [0027], This clearly shows that the cyclodextrin forms part of a composition of multiple ingredients and that Vandercruys provides no teaching with respect to complexation and association of amorphous drug to cyclodextrin complex as provided by the present invention.

In summary, Vandercruys discloses compositions which in addition to the drug and the cyclodextrin mandatorily contain further ingredients (an acid and an organic polymer) which form an integral part of the glass thermoplastic system and do not

reasonably allow one to pick out parts of it and to combine it with other teachings. Consideration of Vandercruys is further prohibited in that it teaches that an acid must be present (in an amount strongly exceeding the amount of the drug) and a person skilled in the art would reasonably expect that the presence of such acid would be detrimental to the stability of cladribine in view of the fact that cladribine is an acid-labile compound.

The secondary references do not supply the deficiencies in the primary reference, Vandercruys.

Schultz (US 6194395) teaches the use of cyclodextrin as a solubilizer and stabilizer of cladribine in aqueous solution only, which is quite different for the invention. As far as solid oral dosage forms are mentioned, such disclosure is limited to solid mixtures of cladribine and cyclodextrin (see column 5, lines 50-58). The Examiner argues that the melt-extruding of the mixture refers to Baert (WO 97/118839) and that, according to Baert, such melt-extruding leads to amorphous material. However, the fact that melt-extruding of cyclodextrin and cladribine might lead to amorphous material does not imply that such material consists of an amorphous inclusion complex of cladribine in cyclodextrin and more than ever does not imply that amorphous free cladribine is associated with amorphous cyclodextrin complex. Amorphousness can also be provided by different arrangements such as by a mixture of the amorphous cladribine and cyclodextrin. Further, a mixture is explicitly taught by Schultz. Indeed, as the Examiner himself has acknowledged on page 4 of the September 11, 2013 Official Action, "Applicant's remarks are persuasive that the mixture taught by Schultz in view of Baert can reasonably be concluded to be the physical mixture, and the comparative evidence provided by Van Axel Castelli is applicable and persuasive."

The Examiner's allegation set forth on page 9, second paragraph, regarding Rendenti et al., that piroxicam/β-cyclodextrin complex prepared by melt-spinning is a physical mixture of amorphous piroxicam and amorphous cyclodextrin supports such view. This is because melt extruding comprises the steps a) mixing of cyclodextrin and active ingredient, c) heating of the mixture until melting of one of the components and e) cooling the mixture till it solidifies (See Baert, page 5 steps a), c) and e)). As piroxicam has the melting point of 205 - 210°C (page 290, right column, line 1) and β-cyclodextrin melts with decomposition of 250°C (page 291, left column, lines 13 - 25), melt-spinning of a piroxicam β-cyclodextrin mixture must also comprise the step of heating of the mixture until melting of one of the components (here piroxicam only, melting of β-cyclodextrin can be excluded as this is accompanied by its decomposition), as described in step c) of Baert for melt extruding.

Further, with respect to instant Claims 5-6 and 29-30, while Baert teaches that ratios of active ingredient to cyclodextrin in their mixtures may vary widely and mentions ratios of 1/100 to 100/1 (page 11, first paragraph), these claims require specific ratios of cladribine to cyclodextrin in the claimed complexes. It is clear that no teaching is given in the art to achieve the technical teaching of the invention, i.e. to provide an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex. The Examiner's calculations as set forth on page 8 are nothing else than cherry picking based on hindsight analysis, using Applicants' own invention as a guide through the maze of Vandercruys, Schultz et al., Baert et al., Rendenti et al. and Pitha et al. This is impermissable "picking and

choosing". Applicants submit that withdrawal of the rejection is in order.

With respect to product-by-process Claims 46-61, these claims afford the same product as that of Claim 1 and are patentable for the same reason that Claim 1 is patentable. Vandercruys does not provide the claimed composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein. The secondary references fail to provide what Vandercruys lacks. The references in combination fail to teach or suggest Applicants' invention.

DOUBLE PATENTING

The Examiner has maintained the double patenting rejection over Claims 1-28 of U.S. Patent No. 7,888,328. Applicants' representative sincerely apologizes for the fact that the Terminal Disclaimer which had been meant to be filed on the same day as the filing of the previous response was inadvertently and unintentionally not filed at that time. Applicants' representative also apologizes for any inconvenience this has caused to the Examiner. An e-Terminal Disclaimer with respect to the '328 patent has now been filed and approved. Therefore, it is believed that the double patenting rejection has now been obviated.

As to *In re Schneller*, 158 USPQ 210 (CCPA 1968), that case was one in which a Terminal Disclaimer had not been filed. Further, Applicants here did in fact present

claims corresponding to those herein in the parent application.

CONCLUSION

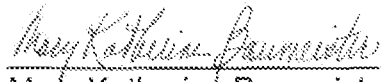
The foregoing remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 19-3140. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to the Deposit Account.

Respectfully submitted,

DENTONS US LLP

Date: December 11, 2013



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Washington, D.C. 20005
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Fax: 202-408-6399

Electronic Acknowledgement Receipt

EFS ID:	17634350
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	11-DEC-2013
Filing Date:	07-JAN-2011
Time Stamp:	18:55:02
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.pdf	109573 8d1518630d8e010d67746cc8b3d2794bb8489dce	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	8

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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
Attorney Docket No.: 20009904-0067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nicholas S. BODOR et al.	)	**MAIL STOP AMENDMENT**
	)	
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
	)	
Filed: January 7, 2011	)	Group Art Unit: 1623
	)	
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100
	)	

SUPPLEMENTAL AMENDMENT IN RESPONSE TO TELEPHONE INTERVIEW

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

Madame:

In supplemental response to the Office Action dated September 11, 2013, please first amend the above-identified patent application as follows:

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Original) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. (Original) The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.

3. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

5. (Original) The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

6. (Original) The composition according to Claim 5, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

7. (Original) The composition according to Claim 1, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

8. (Original) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

9. (Withdrawn) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous

cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

10. (Withdrawn) The method according to Claim 9, wherein the complex is saturated with cladribine.

11. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

12. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

13. (Withdrawn) The method according to Claim 9, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

14. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

15. (Withdrawn) The method according to Claim 9, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on

the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

16. (Withdrawn) The method according to Claim 9, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

17. (Withdrawn-Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

18. (Withdrawn) The method according to Claim 17, wherein the complex is saturated with cladribine.

19. (Canceled)

20. (Withdrawn-Currently Amended) The method according to Claim ~~19~~17, wherein the cladribine-responsive condition is multiple sclerosis.

21. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

22. (Withdrawn) The method according to Claim 17, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

23. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

24. (Withdrawn) The method according to Claim 17, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. (Original) A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

26. (Original) The complex according to Claim 25, saturated with cladribine.

27. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

28. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

29. (Original) The complex according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

30. (Original) The complex according to Claim 29, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

31. (Original) The complex according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

32. (Withdrawn) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 25, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

33. (Withdrawn) The process according to Claim 32, further comprising a filtration step following step (ii).

34. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

35. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

36. (Withdrawn) The process according to Claim 34, wherein step (i) is performed with stirring.

37. (Withdrawn) The process according to Claim 36, wherein step (i) is performed for a period of from about 6 to about 9 hours.

38. (Withdrawn) The process according to Claim 32, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

39. (Withdrawn) The process according to Claim 32, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

40. (Withdrawn) The process according to Claim 39, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

41. (Withdrawn) The process according to Claim 34, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i), or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

42. (Withdrawn) The process according to Claim 41, wherein 825 parts by volume of water are introduced in step (i).

43. (Withdrawn) The process according to Claim 32, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40ºC to about -80ºC for approximately 2 to 4 hours;

(b) a primary drying stage at about -25ºC for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30ºC for approximately 15 to 20 hours.

44. (Withdrawn) The process according to Claim 43, wherein stage (a) of the lyophilization is conducted at about -45ºC for approximately 3 to 4 hours.

45. (Withdrawn) The process according to Claim 43, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

46. (Original) A pharmaceutical composition according to Claim 1, obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80ºC and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

47. (Original) The pharmaceutical composition according to Claim 46, wherein the process further comprises a filtration step following step (i) or (ii).

48. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 60ºC.

49. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 50ºC.

50. (Original) The pharmaceutical composition according to Claim 48, wherein step (i) of the process is performed with stirring.

51. (Original) The pharmaceutical composition according to Claim 50, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

52. (Original) The pharmaceutical composition according to Claim 46, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

53. (Original) The pharmaceutical composition according Claim 46, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80ºC, and held at said temperature for a period of from about 2 to about 4 hours.

54. (Original) The pharmaceutical composition according to Claim 53, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45ºC.

55. (Original) The pharmaceutical composition according to Claim 48, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

56. (Original) The pharmaceutical composition according to Claim 55, wherein 825 parts by volume of water are introduced in step (i) of the process.

57. (Original) The pharmaceutical composition according to Claim 46, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40ºC to about -80ºC for approximately 2 to 4 hours;

(b) a primary drying stage at about -25ºC for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30ºC for approximately 15 to 20 hours.

58. (Original) The pharmaceutical composition according to Claim 57, wherein stage (a) of the lyophilization is conducted at about -45ºC for approximately 3 to 4 hours.

59. (Original) The pharmaceutical composition according to Claim 57, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

60. (Original) The pharmaceutical composition according to Claim 46, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

61. (Original) The pharmaceutical composition according to Claim 60, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

62. - 64. (Canceled)

65. (Withdrawn-Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, wherein administering cladribine is accompanied by administering one or more additional active ingredients for treating the cladribine-responsive condition.

66. (Withdrawn) The method according to Claim 65, wherein the complex is saturated with cladribine.

67. – 68. (Canceled)

69. (Withdrawn) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

70. (Withdrawn) The method according to Claim 66, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

71. – 72. (Canceled)

73. (Withdrawn) The method according to Claim 65, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

74. (Withdrawn) The method according to Claim 69, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

75. (Withdrawn) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

76. (Canceled)

77. (Withdrawn) The method according to Claim 73, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

78. (Withdrawn-Currently Amended) The method according to Claim ~~73~~ 74, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

79. (Withdrawn) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

80. (Withdrawn) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

81. (Withdrawn) The method according to Claim 65, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

82. (Withdrawn) The method according to Claim 75, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

83. (Withdrawn) The method according to Claim 65, wherein the cladribine-responsive condition is multiple sclerosis.

84. (Withdrawn) The method according to Claim 75, wherein the cladribine-responsive condition is multiple sclerosis.

85. (Withdrawn) The method according to Claim 77, wherein the cladribine-responsive condition is multiple sclerosis.

86. (Withdrawn) The method according to Claim 83, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

87. (Withdrawn) The method according to Claim 84, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

88. (Withdrawn) The method according to Claim 85, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

REMARKS

Further examination and consideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the amendments to the claims and following remarks.

STATEMENT OF SUBSTANCE OF TELEPHONE INTERVIEW

The Applicants thank Examiner Lau for the courtesy of the Examiner-initialed telephone interview with the undersigned representative on February 18, 2014.

In the telephone interview, Examiner Lau indicated that the withdrawn method of treatment claims (17-24 and 65-88) could be rejoined and allowed, if the independent method of treatment claims were amended to specify that the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia (as originally specified in Claims 19, 67 and 68). Applicants' representative agreed to make the specified amendment to each of the independent method of treatment claims and to amend their dependent claims consistently with these amendments.

STATUS OF CLAIMS AND DISCUSSION OF AMENDMENTS

Claims 1-18, 20-61, 65-66, 69-70, 73-75 and 77-88 are now in this application. By the foregoing amendment, Claims 17, 20, 65 and 78 have been amended; and Claims 19, 67-68, 71-72 and 76 have been canceled as redundant in light of the amendment of the independent method of treatment claims. Claim 20 has been

amended so that it no longer depends from a canceled claim. The dependency of Claim 78 has also been corrected; because of a typographical error, it was originally duplicative of Claim 77.

It is clear from the foregoing that no new matter has been introduced by these claim amendments and that the amendments place the method of treatment claims in rejoinable and allowable form.

CONCLUSION

The foregoing remarks and amendments are being made to place the method of treatment claims in the application in condition for rejoinder and allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should a further interview be helpful to expedite prosecution of this application, the Examiner is invited to telephone the undersigned as soon as possible.

If there are any additional fees due in connection with the filing of this response, please charge the fees to counsel's Deposit Account No. 19-3140. If a fee is required

for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to counsel's Deposit Account.

Respectfully submitted,

DENTONS US LLP

Date: February 20, 2014

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Electronic Acknowledgement Receipt

EFS ID:	18248155
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Louie Malloy
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	20-FEB-2014
Filing Date:	07-JAN-2011
Time Stamp:	09:09:10
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		0067SuppAmdt.pdf	180392 224c3b7e8b1fdf7d59900df2c6bdf960ee7c2e5c	yes	20

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	17
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New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/986,310	Filing Date 01/07/2011	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT **02/20/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 79	Minus	** 85	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

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

LIE
/Davina Butler/

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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EXAMINER
LAU, JONATHAN S

ART UNIT	PAPER NUMBER
1673	

DATE MAILED: 03/13/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/13/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

13974 7590 03/13/2014
DENTONS US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/13/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1673	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

13974 7590 03/13/2014

DENTONS US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1673	

DATE MAILED: 03/13/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 172 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 172 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/986,310	Applicant(s) BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1673	AIA (First Inventor to File) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *See Continuation Sheet*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-18,20-61,65,66,69,70,73-75 and 77-88*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 4 pg
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *1 pg* .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1673

Continuation of Item 1. This communication is responsive to : Applicant's Amendment and Remarks, filed 11 Dec 2013, and Applicant's Supplement Amendment and Remarks, filed 20 Feb 2014.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 11 Dec 2013, and Applicant's Supplement Amendment and Remarks, filed 20 Feb 2014, in which claims 17, 20, 65 and 78 are amended and claims 19, 67, 68, 71, 72 and 76 are canceled.

Applicant's Supplement Amendment and Remarks, filed 20 Feb 2014, will be entered because the amendment is deemed to place the application in condition for allowance.

This application is a domestic application, filed 7 Jan 2011; and claims benefit as a CON of 10/551,205, issued as Patent 7,888,328, which is a 371 of PCT/US2004/009387, filed 26 Mar 2004, which claims benefit of provisional application 60/458,922, filed 28 Mar 2003, and claims benefit of provisional application 60/484,756, filed 2 Jul 2003, and claims benefit of provisional application 60/541,247, filed 4 Feb 2004. The filing date of the instant claims is deemed to be provisional application 60/541,247, filed 4 Feb 2004.

Claims 1-18, 20-61, 65, 66, 69, 70, 73-75 and 77-88 are pending in the current application. Claims 9-18, 20-24, 32-45, 65, 66, 69, 70, 73-75 and 77-88, drawn to non-elected inventions, are rejoined herein. Claims 1-18, 20-61, 65, 66, 69, 70, 73-75 and 77-88 are allowed herein.

Terminal Disclaimer

The terminal disclaimer filed on 10 Dec 2013 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 7,888,328 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Election/Restrictions

Claims 1-8, 25-31 and 46-61 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 9-18, 20-24, 32-45, 65, 66, 69, 70, 73-75 and 77-88, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 8 Nov 2012 is hereby withdrawn**. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the

limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Rejections Withdrawn

Applicant's Remarks, filed 11 Dec 2013, with respect that claims 1-8, 25-31 and 46-61 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Vandercruys (US Patent Application Publication 2002/0150616, published 17 Oct 2002, filed 27 May 1998, cited in PTO-892) in view of Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, provided by Applicant in IDS mailed 7 Jan 2011), Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record), Redenti et al. (Int. J. Pharm., 1996, 129, p289-294, cited in PTO-892), and Pitha et al. (Life Sci., 1998, 43, p493-502, cited in PTO-892) has been fully considered and is persuasive, as Applicant's remarks are persuasive that Vandercruys requires the essential feature of a physiologically tolerable water-soluble acid which preferably gives a pH 2 (abstract and page 3, paragraph 0028-0029) and that cladribine is known to be acid-labile, for example as a adenosine analog subject to acid-catalyzed glycolysis. While Vandercruys includes cladribine in an extensive list of possible drugs at paragraph 0070 spanning

pages 4-5, Vandercruys does not disclose a working example of the invention of Vandercruys wherein the sparingly water-soluble drug is an acid-labile drug such as an adenosine analog. Further, Applicant's remarks of record, filed 28 May 2013, suggest unpredictability with regard to specifically the amorphous cladribine-cyclodextrin complex as taught by Shultz and Baert. Therefore applicant's remarks are persuasive that there is no reasonable expectation of success to combine Vandercruys in view of Schultz et al., Baert et al., Redenti et al., and Pitha et al. in a manner to render obvious the instant invention as claimed. The instant invention as claimed is not taught or fairly suggested with a reasonable expectation of success by the closest prior art.

This rejection has been **withdrawn**.

Applicant's terminal disclaimer, filed 10 Dec 2013, with respect that claims 1-8, 25-31 and 46-61 are rejected on the ground of nonstatutory double patenting over claims 1-28 of U. S. Patent No. 7,888,328 has been fully considered and is persuasive, as the terminal disclaimer has been recorded.

This rejection has been **withdrawn**.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is (571)270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHAOJIA ANNA JIANG/
Supervisory Patent Examiner, Art Unit 1673

/Jonathan S Lau/
Examiner, Art Unit 1673

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/986,310	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1673	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jonathan S. Lau*. (3)_____.

(2) *Mary Katherine Baumeister*. (4)_____.

Date of Interview: *18 February 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: *none*.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *17 and 65*.

Identification of prior art discussed: *none*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The product claims were indicated as allowable, and rejoinder of the withdrawn method claims was discussed. The breadth of the claim language of "cladribine-responsive condition" in claims 17 and 65 would likely raise issues of written description or scope of enablement if rejoined. In order to facilitate allowance of the application, incorporating specific conditions of claims 19, 67 and 68 into claims 17 and 65 was discussed.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

Substitute for form 1449/PTO & 1449B/PTO

FIRST
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known

Application Number	12/986310
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-4,383,992	05-17-1983	Lipari	
	US-6,239,118 B1	05-29-2001	Shatz et al.	
	US-5,424,296	06-13-1995	Saven et al.	
	US-5,510,336	04-23-1996	Saven et al.	
	US-5,506,214	04-09-1996	Beutler	
	US-4,659,696	04-21-1987	Hirai et al.	
	US-3,459,731	08-05-1969	Gramera et al.	
	US-4,478,995	10-23-1984	Shinoda et al.	
	US-5,310,732	05-10-1994	Carson et al.	
	US-5,401,724	03-28-1995	Beutler	
	US-5,106,837	04-21-1992	Carson et al.	
	US-4,497,803	02-05-1985	Harada et al.	
	US-6,194,395 B1	02-27-2001	Schultz et al.	
	US-6,407,079 B1	06-18-2002	Müller et al.	
	US-4,870,060	09-26-1989	Müller	
	US-4,727,064	02-23-1988	Pitha	
	US-4,596,795	06-24-1986	Pitha	
	US-4,764,604	08-16-1988	Müller	
	US-4,535,152	08-13-1985	Szejtli et al.	
	US-6,174,873	01-16-2001	Wrenn, Jr. et al.	
	US-6,699,849	03-02-2004	Loftsson et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	
	EP 0 197 571 A2	10-15-1986	Janssen Pharmaceutica N.V.							X	
	WO 90/12035A1	10-18-1990	Janssen Pharmaceutica N.V.							X	
	DE 31 18 218 A1	04-22-1982	Chinoin Gyogyszer Es Vegyeszet						X	X	
	DE 33 17 064 A1	11-15-1984	Consortium Elektrochem Ind						X	X	
	GB 2 189 245 A	10-21-1987	American Maize-Products Company							X	
	EP 0 149 197 B1	07-24-1985	Janssen Pharmaceutica N.V.	X						X	
	EP 0 094 157 A1	11-16-1983	Janssen Pharmaceutica N.V.							X	
	WO 99/42111	08-26-1999	Cyclops, ehf								

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 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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FIRST INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 4

Complete if Known	
Application Number	12/986310
Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

FOREIGN PATENT DOCUMENTS

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	TARASIUK et al., "Stability of 2-Chloro-2'-Deoxyadenosine at Various pH and Temperature", *Archivum Immunologiae et Therapiae Experimentalis*, Vol. 42, pp. 13-15, 1994, published by Birkhauser Publishers Ltd., Basel, Switzerland
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Sheet 3 of 4

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	BAKTHIAR et al., "A study of the complexation between dimethyl-β-cyclodextrin and steroid hormones using electrospray ionization mass spectrometry", *Rapid Communications in Mass Spectrometry*, Vol. 11, pp. 1478-1481, 1997, John Wiley And Sons Ltd, England
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Sheet 4 of 4

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Filing Date	January 5, 2011
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000067

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	OTHER
	International Search Report dated October 12, 2004 for PCT/US2004/009387, filed March 26, 2004
	PCT International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2004/009387, International Filing date March 26, 2004.

Examiner Signature	/Jonathan Lau/	Date Considered	03/06/2014

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1673

CPC						
Symbol					**Type**	**Version**
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/JONATHAN S LAU/ Examiner.Art Unit 1673	02/25/2014	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	79	
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1673		O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
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	JONATHAN S LAU	1673

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
514	46	A	6	1	K	31 / 7076 (2006.01.01)										
CROSS REFERENCE(S)		A	6	1	K	47 / 40 (2006.01.01)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
514	58															

/JONATHAN S LAU/ Examiner.Art Unit 1673 (Assistant Examiner)	02/25/2014 (Date)	**Total Claims Allowed:** 79	
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1673 (Primary Examiner)	(Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12986310	BODOR ET AL.
	Examiner	**Art Unit**
	JONATHAN S LAU	1673

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
22	1	54	17	9	33	37	49	61	65	77	81				
23	2	55	18	10	34	33	50	62	66	74	82				
24	3		19	11	35	34	51		67	78	83				
25	4	56	20	12	36	38	52		68	75	84				
26	5	57	21	13	37	39	53	64	69	69	85				
27	6	58	22	14	38	40	54	63	70	79	86				
28	7	59	23	15	39	35	55		71	76	87				
29	8	60	24	16	40	36	56		72	70	88				
46	9	1	25	17	41	41	57	67	73						
47	10	2	26	18	42	42	58	65	74						
48	11	3	27	19	43	43	59	71	75						
49	12	4	28	20	44	44	60		76						
50	13	5	29	21	45	45	61	68	77						
51	14	6	30	30	46		62	66	78						
52	15	7	31	31	47		63	72	79						
53	16	8	32	32	48		64	73	80						

/JONATHAN S LAU/ Examiner.Art Unit 1673	02/25/2014	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	79	
/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1673		O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1463	514/46.ccls.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:47
L2	1423	514/58.ccls.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:48
L3	56	2 and cladribine	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:48
L4	91	1 and cladribine	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:48
L5	58	4 and (cyclodextrin or complex)	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:48
L6	1692	a61k31/7076.cpc.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:50
L7	1416	a61k47/40.cpc. or a61k47/48969.cpc.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:52
L8	19	6 and 7	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:52
L9	49	3 and amorphous	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:52
L10	12	5 and amorphous	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:52
L13	36	cladribine.ti,ab.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:57
L14	15	13 AND ((A61K31/7076 OR A61K31/724 OR A61K47/40 OR A61K9/205).CPC.)	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:58
L15	11	A61K31/7076.cpc. and (A61K31/724 OR A61K47/40 OR A61K9/205).CPC.	US-PGPUB; USPAT; USOCR	NEAR	ON	2014/02/25 15:59

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L11	0	514/58.ccls.	UPAD	NEAR	ON	2014/02/25 15:56
L12	1	514/46.ccls.	UPAD	NEAR	ON	2014/02/25 15:56

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OK TO ENTER: /J.L./

02/25/2014

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Original) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. (Original) The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.

3. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. (Original) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

5. (Original) The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

6. (Original) The composition according to Claim 5, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

7. (Original) The composition according to Claim 1, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

8. (Original) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

9. (Withdrawn) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous

cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

10. (Withdrawn) The method according to Claim 9, wherein the complex is saturated with cladribine.

11. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

12. (Withdrawn) The method according to Claim 9, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

13. (Withdrawn) The method according to Claim 9, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

14. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

15. (Withdrawn) The method according to Claim 9, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on

the curve of a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

16. (Withdrawn) The method according to Claim 9, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

17. (Withdrawn-Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

18. (Withdrawn) The method according to Claim 17, wherein the complex is saturated with cladribine.

19. (Canceled)

20. (Withdrawn-Currently Amended) The method according to Claim ~~19~~17, wherein the cladribine-responsive condition is multiple sclerosis.

21. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

22. (Withdrawn) The method according to Claim 17, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

23. (Withdrawn) The method according to Claim 17, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

24. (Withdrawn) The method according to Claim 17, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. (Original) A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

26. (Original) The complex according to Claim 25, saturated with cladribine.

27. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

28. (Original) The complex according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

29. (Original) The complex according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

30. (Original) The complex according to Claim 29, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

31. (Original) The complex according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

32. (Withdrawn) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 25, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

33. (Withdrawn) The process according to Claim 32, further comprising a filtration step following step (ii).

34. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

35. (Withdrawn) The process according to Claim 32, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

36. (Withdrawn) The process according to Claim 34, wherein step (i) is performed with stirring.

37. (Withdrawn) The process according to Claim 36, wherein step (i) is performed for a period of from about 6 to about 9 hours.

38. (Withdrawn) The process according to Claim 32, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

39. (Withdrawn) The process according to Claim 32, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

40. (Withdrawn) The process according to Claim 39, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

41. (Withdrawn) The process according to Claim 34, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i), or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

42. (Withdrawn) The process according to Claim 41, wherein 825 parts by volume of water are introduced in step (i).

43. (Withdrawn) The process according to Claim 32, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40ºC to about -80ºC for approximately 2 to 4 hours;

(b) a primary drying stage at about -25ºC for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30ºC for approximately 15 to 20 hours.

44. (Withdrawn) The process according to Claim 43, wherein stage (a) of the lyophilization is conducted at about -45ºC for approximately 3 to 4 hours.

45. (Withdrawn) The process according to Claim 43, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

46. (Original) A pharmaceutical composition according to Claim 1, obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80ºC and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

47. (Original) The pharmaceutical composition according to Claim 46, wherein the process further comprises a filtration step following step (i) or (ii).

48. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

49. (Original) The pharmaceutical composition according to Claim 46, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

50. (Original) The pharmaceutical composition according to Claim 48, wherein step (i) of the process is performed with stirring.

51. (Original) The pharmaceutical composition according to Claim 50, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

52. (Original) The pharmaceutical composition according to Claim 46, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

53. (Original) The pharmaceutical composition according Claim 46, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80ºC, and held at said temperature for a period of from about 2 to about 4 hours.

54. (Original) The pharmaceutical composition according to Claim 53, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45ºC.

55. (Original) The pharmaceutical composition according to Claim 48, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process, or wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

56. (Original) The pharmaceutical composition according to Claim 55, wherein 825 parts by volume of water are introduced in step (i) of the process.

57. (Original) The pharmaceutical composition according to Claim 46, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40ºC to about -80ºC for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

58. (Original) The pharmaceutical composition according to Claim 57, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

59. (Original) The pharmaceutical composition according to Claim 57, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

60. (Original) The pharmaceutical composition according to Claim 46, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

61. (Original) The pharmaceutical composition according to Claim 60, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

62. - 64. (Canceled)

65. (Withdrawn-Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, wherein administering cladribine is accompanied by administering one or more additional active ingredients for treating the cladribine-responsive condition.

66. (Withdrawn) The method according to Claim 65, wherein the complex is saturated with cladribine.

67. – 68. (Canceled)

69. (Withdrawn) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

70. (Withdrawn) The method according to Claim 66, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

71. – 72. (Canceled)

73. (Withdrawn) The method according to Claim 65, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

74. (Withdrawn) The method according to Claim 69, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

75. (Withdrawn) The method according to Claim 65, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

76. (Canceled)

77. (Withdrawn) The method according to Claim 73, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

78. (Withdrawn-Currently Amended) The method according to Claim ~~73~~ 74, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

79. (Withdrawn) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

80. (Withdrawn) The method according to Claim 75, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

81. (Withdrawn) The method according to Claim 65, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

82. (Withdrawn) The method according to Claim 75, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

83. (Withdrawn) The method according to Claim 65, wherein the cladribine-responsive condition is multiple sclerosis.

84. (Withdrawn) The method according to Claim 75, wherein the cladribine-responsive condition is multiple sclerosis.

85. (Withdrawn) The method according to Claim 77, wherein the cladribine-responsive condition is multiple sclerosis.

86. (Withdrawn) The method according to Claim 83, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

87. (Withdrawn) The method according to Claim 84, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

88. (Withdrawn) The method according to Claim 85, wherein one or more additional active ingredients for treating multiple sclerosis is/are selected from the group consisting of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, 4-aminopyridine and amantadine.

Google cladribine OR adenosine cyclodextrin amorphous complex OR inclusion

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Drug solubilizers to aid pharmacologists: **amorphous cyclodextrin** derivatives
J Pitha, T Irie, PB Sklar, JS Nye - Life sciences, 1988 - Elsevier
... ligand, anxiogenic agent 1.1 antipsychotic dopamine antagonist 10 **adenosine** antagonist, antiasthmatic ... are often bi-phasic, that is, 502 Solubilization by **Amorphous Cyclodextrins** Vol. ... above mixtures contain hundreds of isomeric and enantiomeric **cyclodextrin** derivatives there ...
Cited by 207 Related articles All 4 versions Cite Save

Pharmaceutical preparations containing **cyclodextrin** derivatives
J Pitha - US Patent 4,727,064, 1988 - Google Patents
... a stablizing **amorphous complex** of a drug and a mixture of **cyclodextrins** which comprises the steps of: 1. Dissolving an intrinsically **amorphous** mixture of **cyclodextrin** deratives which are water soluble and capable of forming **inclusion** complexes with drugs in water; and. ...
Cited by 239 Related articles All 2 versions Cite Save

Pharmaceutical compositions containing drugs which are instable or sparingly soluble in water and methods for their preparation
BW Müller, U Brauns - US Patent 6,407,079, 2002 - Google Patents
... Mar 26, 2004, Jan 12, 2011, Ares Trading SA, Oral formulations of **cladribine**. ... Daniel B. Carr, Formulations of low dose non-steroidal anti-inflammatory drugs and beta-**cyclodextrin**. WO2008088816A1 *, Jan 16, 2008, Jul 24, 2008, **Adenosine** Therapeutics, Llc, **Adenosine** ...
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In vivo and In vitro Correlation for Delayed release Behaviour of a Molsidomine/O carboxymethyl O ethyl β **cyclodextrin Complex** in Gastric Acidity controlled ...
T HORIKAWA, F HIRAYAMA... - Journal of pharmacy and ..., 1995 - Wiley Online Library
... Omeprazole, an H+, K+-**adenosine** triphosphatase inhibi- tor, was donated by Yoshitomi Pharmaceutical Ind ... of l-hexylcarbamoyl-5-fluorouracil (HCFU) by 0-carboxymethyl-0-ethyl-P-**cyclodextrin**. ... Miiller, B. W., Brauns, U. (1985) Solubilization of drugs by modified P-**cyclodextrins**. ...
Cited by 22 Related articles All 4 versions Cite Save

Pharmaceutical applications of **cyclodextrins**. 1. Drug solubilization and stabilization [PDF] from researchgate.net
T Loftsson, ME Brewster - Journal of pharmaceutical sciences, 1996 - Wiley Online Library
... β-CD **Adenosine** 7 −21 −53 32 ... been moved away from the cavity by a butyl ether spacer group, is an excellent solubilizer.71 (Carboxymethyl)-β-**cyclodextrin** is another in- teresting anionic **cyclodextrin** derivative.72 Compared to neutral **cyclodextrins**, enhanced complexation ...
Cited by 1534 Related articles All 6 versions Cite Save

Subject Index to Volume 18 (2001)
AN Drug, A Adenosine - Pharmaceutical Research, 2001 - Springer
... Crystallization, macromolecular, 1483 Crystallization, supercritical fluid, 852 Cyclic **adenosine** monophosphate (cAMP), 1651 Cyclic voltammetry, 702 **Cyclodextrins**, 667, 886 ... 1455 Hydrophobic drugs, 510 Hydrophobicity, 104 Hydropropyl **cyclodextrin**, 667 Hydroxyethyl ...

All 3 versions Cite Save

Method and compositions for solubilization and stabilization of polypeptides, especially proteins
MS Hora, J Rubinfeld, W Stern, GJ Wong - US Patent 5,730,969, 1998 - Google Patents
... 2) in increasing concentrations (percent w/v) of hydroxypropyl-β-**cyclodextrin** (HPBCD ... affect their biological function, aqueous solubility and ability to interact with the **cyclodextrins**. ... of proteins and immobilized proteases), cell surface recognition proteins (**adenosine** and analogs ...
Cited by 28 Related articles All 5 versions Cite Save

Role of cyclic **adenosine** 3', 5'-monophosphate and serum albumin in head-to-head agglutination of boar spermatozoa
H Harayama, M Miyake, S Kato - Reproduction, Fertility and Development, 2001 - CSIRO
... mKRB, modified Krebs-Ringer bicarbonate; mKRB-P, mKRB containing 0.1% polyvinyl alcohol; BSA, bovine serum albumin; dbcAMP, dibutyryl cyclic **adenosine** 3',5'-monophosphate; MBC, methyl-β-**cyclodextrin**. Page 10. Mechanism of sperm agglutination 315 ...
Cited by 14 Related articles All 7 versions Cite Save

Improvement of gliquidone hypoglycaemic effect in rats by **cyclodextrin** formulations [PDF] from researchgate.net
A Miro, E Quaglia, U Sorrentino, MI La Rotonda... - European journal of ..., 2004 - Elsevier
... These compounds display similar chemical features and seem to act by blocking the pancreatic islet β-cell **adenosine** 5'triphosphate (ATP ... Pharmaceutical applications of **cyclodextrins**. ... Physico-chemical and pharmacological properties of nimesulide/β-**cyclodextrin** formulations. ...
Cited by 15 Related articles All 6 versions Cite Save

Cyclodextrin complexes of benzodiazepines
T Loftsson, M Masson, E Stefansson - US Patent 6,699,849, 2004 - Google Patents
... isomeric products, chemical modification can transform the crystalline **cyclodextrins** into **amorphous** mixtures increasing ... In aqueous solutions, **cyclodextrins** form complexes with many drugs through a process ... Once included in the **cyclodextrin** cavity, the drug molecules may be ...
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	12986310	BODOR ET AL.
	Examiner	Art Unit
	JONATHAN S LAU	1623

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/7076	2/25/2014	JSL
A61K 47/40, 47/48969	2/25/2014	JSL

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	46, 58	2/25/2014	JSL

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor, Yogesh Dandiker)	2/15/2013	JSL
EAST - see attached notes	2/15/2013	JSL
Google Scholar - see attached notes	2/15/2013	JSL
Google Scholar - see attached notes	9/3/2013	JSL
EAST - inventor name search (Nicholas Bodor, Yogesh Dandiker) - updated	2/25/2014	JSL
Review prosecution history of parent case 10/551205	2/25/2014	JSL
Google Scholar - see attached notes	2/25/2014	JSL

INTERFERENCE SEARCH			
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

13974 7590 04/17/2014

DENTONS US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1673	

NOTIFICATION DATE	DELIVERY MODE
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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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Application No. : 12986310
Applicant : Bodor
Filing Date : 01/07/2011
Date Mailed : 04/17/2014

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

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Application No. 12986310

IDENTIFICATION OF APPLICATION DEFICIENCIES

☐ Applicant must provide legible text for the following item(s).

- ☐ Specification filed , page(s) .
- ☐ Claims filed , claim(s) .
- ☐ Oath/declaration filed .
- ☐ Other: .

☐ Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.

☒ The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.page 23, lines 25 and 27

☐ Applicant must provide an Abstract of the Disclosure.

☐ Applicant has submitted a DECLARATION (37 CFR 1.63) FOR A UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) (e.g., form PTO/SB/01A). The Application Data Sheet, however, is not present with the filed application. Applicant must submit an Application Data Sheet or file a new oath or declaration (e.g., PTO/SB/01) executed by the inventors and containing the information required in 37 CFR 1.63.

☐ Applicant must provide an executed declaration.

☐ Applicant must provide the missing page(s) of the oath/declaration or Application Data Sheet filed

☐ Applicant must provide a declaration signed by inventor(s) .

☐ The oath/declaration filed shows non-initialed and/or non-dated alterations. Applicant must file a new oath/declaration in compliance with 37 CFR 1.67(a).

☐ Applicant(s) in the latest-filed oath/declaration or Application Data Sheet (ADS) did not show the inventor's residence at all, or did not show both a city and state in the U.S. inventor's residence, or did not show both a city and country in the non-U.S. inventor's residence. Applicant must supply an oath/declaration or Application Data Sheet (ADS) that shows each U.S. inventor's city and state of residence and each non-U.S. inventor's city and country of residence.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nicholas S. BODOR et al.	)	**MAIL STOP ISSUE FEE**
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
Filed: January 7, 2011	)	Group Art Unit: 1623
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100

REPLY AND AMENDMENT PURSUANT TO 37 C.F.R. § 1.312

In response to the Notice to File Corrected Application Papers dated April 17, 2014, Applicants hereby submit the following amendment and remarks pursuant to 37 C.F.R. §1.312.

AMENDMENTS TO THE SPECIFICATION:

Please replace page 23 of the as-filed specification with the attached new page 23, which deleted the final sentence in the paragraph at lines 7-29.

Attached: Marked-Up and Clean Copies of Page 23

REMARKS

After allowance of this application, it was noted that page 23 of the as-filed specification contained references to applications for which no application numbers were given. These were provisional applications which were abandoned without the filing of non-provisional applications based thereon. Further, they were not for inventions of the present inventors and belonged to a former assignee. They were not made available to the public. In the parent case, now patented (Application No. 12/986, 310), the sentence in question was deleted during prosecution, by an amendment made October 3, 2008. Accordingly, page 23 of the specification has been amended to delete the final sentence on page 23, consistent with the parent.

This amendment was not proposed sooner because it was not realized that the error had not been corrected until after allowance. This amendment does not raise any new issues and thus is appropriate at this time. Entry is respectfully requested.

Respectfully submitted,

DENTONS US LLP

Date: June 12, 2014

/Mary Katherine Baumeister/
Mary Katherine Baumeister
Registration No. 26254

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Dentons US LLP
1301 K Street NW, Suite 600, East Tower
Washington, D.C. 20005
Phone: 202-408-9186
Fax: 202-408-6399

Physicians, Vol. 111, No. 1, 35-44 (1999); Selby et al., *The Canadian Journal of Neurological Sciences*, 25, 295-299 (1998); Tortorella et al., *Current Opinion in Investigational Drugs*, 2 (12), 1751-1756 (2001); Rice et al., *Neurology*, 54, 1145-1155 (2000); and Karlsson et al., *British Journal of Haematology*, 116, 538-548 (2002); all of which are incorporated by reference herein in their entireties and relied upon.

Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability obtain after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. ~~For further dosing information, see also U.S. Provisional Patent Application No. _____ [IVAX0021-P-USA/Attorney Docket No. 033935-011], and U.S. Provisional Patent Application No. _____ [IVAX0022-P-USA/Attorney Docket No. 033935-012], both entitled "Cladribine Regimen for Treating Multiple Sclerosis", both filed on March 25, 2004 and incorporated by reference herein in their entireties.~~

Physicians, Vol. 111, No. 1, 35-44 (1999); Selby et al., *The Canadian Journal of Neurological Sciences*, 25, 295-299 (1998); Tortorella et al., *Current Opinion in Investigational Drugs*, 2 (12), 1751-1756 (2001); Rice et al., *Neurology*, 54, 1145-1155 (2000); and Karlsson et al., *British Journal of Haematology*, 116, 538-548 (2002); all of which are incorporated by reference herein in their entireties and relied upon.

Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability obtain after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment.

Electronic Acknowledgement Receipt

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Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Mary Katherine Baumeister/Rebecca Brimmer
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	20009904-0067
Receipt Date:	12-JUN-2014
Filing Date:	07-JAN-2011
Time Stamp:	18:18:08
Application Type:	Utility under 35 USC 111(a)

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	Specification	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	3
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/13/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1673	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
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5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /MARTIN A. BRUEHS/ Date JUNE 13, 2014
Typed or printed name MARTIN A. BRUEHS Registration No. 45635

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	12986310
Filing Date:	07-Jan-2011
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Martin A. Bruehs/Louie Malloy
Attorney Docket Number:	20009904-0067

Filed as Large 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:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Printed Copy of Patent - No Color	8001	4	3	12
		Total in USD ($)		**972**

Electronic Acknowledgement Receipt

EFS ID:	19296893
Application Number:	12986310
International Application Number:	
Confirmation Number:	6100
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	13974
Filer:	Martin A. Bruehs/Louie Malloy
Filer Authorized By:	Martin A. Bruehs
Attorney Docket Number:	20009904-0067
Receipt Date:	13-JUN-2014
Filing Date:	07-JAN-2011
Time Stamp:	11:55:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$972
RAM confirmation Number	9528
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		455			

1	Issue Fee Payment (PTO-85B)	0067IssueFee.pdf	138250 2eb3403798e7695bcf1f5c91bac8a384bf3f2c9f	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31792 51ca62ba91c449063c4ba5d750bf4cf06af2f90f	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	170042	

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.

OK TO ENTER: /J.L./

06/17/2014

PATENT
Attorney Docket No.: 20009904-0067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nicholas S. BODOR et al.	)	**MAIL STOP ISSUE FEE**
	)	
Application No.: 12/986,310	)	Examiner: Jonathan S. LAU
	)	
Filed: January 7, 2011	)	Group Art Unit: 1623
	)	
Title: ORAL FORMULATIONS OF CLADRIBINE	)	Confirmation No.: 6100
	)	

REPLY AND AMENDMENT PURSUANT TO 37 C.F.R. § 1.312

In response to the Notice to File Corrected Application Papers dated April 17, 2014, Applicants hereby submit the following amendment and remarks pursuant to 37 C.F.R. §1.312.

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.
12/986,310	01/07/2011	Nicholas S. Bodor	20009904-0067	6100

13974 7590 06/25/2014

DENTONS US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1673	

NOTIFICATION DATE	DELIVERY MODE
06/25/2014	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

martin.bruehs@dentons.com
patents.us@dentons.com

Response to Rule 312 Communication	Application No.	Applicant(s)
	12/986,310	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S. Lau	1673

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

1. ☒ The amendment filed on *12 June 2014* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

The specification is amended to omit that which is well-known to those skilled in the art. Therefore this amendment is directed to matters of form not affecting the scope of the invention.

/SHAOJIA ANNA JIANG/ Supervisory Patent Examiner, Art Unit 1673	/Jonathan S Lau/ Examiner, Art Unit 1673

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/986,310	07/22/2014	8785415	20009904-0067	6100

13974 7590 07/02/2014

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Chicago, IL 60606-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 357 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Nicholas S. Bodor, Bal Harbour, FL;
Yogesh Dandiker, Toronto, CANADA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.