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(54) Title: NEW SEXUAL-DYSFUNCTION-COMPOUND-CONTAINING RAPID-ONSET PHARMACEUTICAL FORMULATIONS COMPRISING COCOA POWDER AND USE THEREOF

(57) Abstract: A sexual-dysfunction-compound-containing rapid-onset pharmaceutical composition that comprises cocoa powder, process for manufacturing the composition and use of the composition in sexual dysfunction therapy.

New sexual-dysfunction-compound-containing rapid-onset pharmaceutical formulations comprising cocoa powder and use thereof

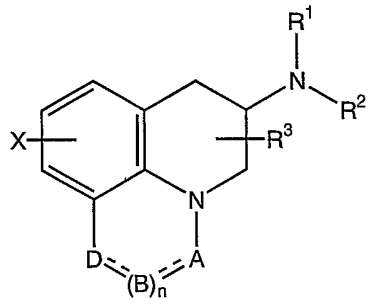
Field of the Invention

This invention relates to novel rapid-onset orally administered pharmaceutical compositions of sexual dysfunction (SD) compounds and use thereof. More particularly, the present invention relates to compositions comprising SD compounds and cocoa powder, methods to prepare said compositions, and to methods for using said compositions in sexual dysfunction therapy, including enhancement of sexual desire, and interest or performance.

Background and Prior Art

Orally administered therapies for sexual dysfunction, in particular for male erectile disorder, are well known. See for example Gingell & Lockyer (1999), "Emerging pharmacological therapies for erectile dysfunction", Expert Opinion on Therapeutic Patents 9, 1689-1696. Drugs in use or in development include phosphodiesterase type 5 (PDE5) inhibitors, *e.g.*, sildenafil citrate, available under the trademark Viagra® of Pfizer, cyclic AMP activators, α-adrenergic antagonists, *e.g.*, yohimbine, and dopaminergic agonists, *e.g.*, apomorphine.

International Patent Publication No. WO 00/40226 discloses compounds useful in treating sexual dysfunction in men and women, these compounds being of formula (I)



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

with various provisos indicated therein. WO 00/40226 further contemplates prescription of the drug (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one (*Z*)-2-butenedioate (1:1) to male and female subjects at a dose of 1-3 mg, to be taken 0.5-1 h before engaging in sexual activity, and indicates that at such a dose and timing of administration the drug is therapeutically effective. No information is provided as to the route of administration or nature of dosage form.

The class of compounds proposed for treatment of sexual dysfunction in WO 00/40226 was earlier disclosed in U.S. Patent No. 5,273,975 to Moon *et al.* to have therapeutically useful central nervous system activity. Certain compounds of the above class are the subject of a paper by Heier *et al.* (1997), "Synthesis and biological activities of (*R*)-5,6-dihydro-N,N-dimethyl-4H-imidazo[4,5,1-*ij*]quinolin-5-amine and its metabolites", J. Med. Chem. 40, 639-646.

In spite of the availability of sildenafil citrate, apomorphine and other drugs in orally deliverable form, there remains a need for dosage forms of a therapeutic agent for treating sexual dysfunction in men and women, having one or more of the following benefits:

(a) rapid absorption leading to rapid onset of therapeutic effect;

(b) reduced unpleasantness of taste;

(c) no requirement to be taken with water;

(d) high bioavailability for substances with high first pass metabolism;

(e) provision for an association of pleasure; and

(f) no immediate patient-perceived association with medicines.

In one aspect, sexual dysfunction as addressed herein comprises sexual disorders including, without limitation, hypoactive sexual desire disorder, female sexual arousal disorder, male erectile disorder, female orgasmic disorder and male orgasmic disorder, all as defined in Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (1994), and DSM-IV Guidebook (1995), both published by American Psychiatric Press, Inc., Washington, DC.

In another aspect, sexual dysfunction as addressed herein comprises diminish-

ment of sexual desire, interest and/or function arising from primary diseases or conditions that are not sexual disorders in a strict sense. Such diseases and conditions include, without limitation, epilepsy, craniopharyngioma, hypogonadism and general psychiatric disorders such as depression. Sexual dysfunction as addressed herein additionally comprises sexual deficiencies following hysterectomy and/or oophorectomy as well as those arising as side effects of medication.

European Patent Application No. 0 960 621 discloses that sildenafil citrate has an unpleasant taste that cannot be completely masked by flavoring agents, and proposes rapidly disintegrating oral dosage forms of sildenafil in the form of its free base, which has extremely low solubility in water and is virtually tasteless.

International Patent Publication No. WO 99/66933 proposes intranasal administration of sildenafil, illustratively in the form of salts such as the hydrochloride salt, for treatment of erectile dysfunction. Dosage forms proposed include a nasal spray and an aqueous nasal gel. Aqueous solutions are said to be preferred. Rapid onset of therapeutic effect is contemplated; however, no solution is suggested to the problem of unpleasant taste arising from drainage of the drug into the mouth. Further, intranasal administration is not a sufficiently discreet way of administering SD compounds. Dosage rates are contemplated in WO 99/66933 to be lower than are required when the drug is orally administered; a 30 mg dose of sildenafil hydrochloride in the form of a nasal spray is exemplified. Also exemplified is a nasal spray formulation delivering 30 mg of sildenafil hydrochloride and 1 mg of apomorphine hydrochloride.

European Patent Application No. 0 992 240 discloses cGMP-PDE inhibitory compounds said to be useful in treatment of male erectile dysfunction and proposes transmucomembranous administration, for example in the form of sublingual preparations, of such compounds.

International Patent Publication No. WO 00/76509 also proposes nasal administration of apomorphine, illustratively as its hydrochloride salt.

Heaton (1996), "Buccal apomorphine", J. Urol. 155, 49, reports efficacy of a sublingual formulation of apomorphine in treatment of male non-organic erectile dysfunction.

U.S. Patent No. 5,985,889 to El-Rashidy *et al.* proposes sublingual administration of apomorphine for treatment of male psychogenic erectile dysfunction. Various sublingual tablet formulations of apomorphine hydrochloride are disclosed therein.

International Patent Publication No. WO 00/35457 proposes use of apomorphine

for treatment of male organic, *e.g.*, vasculogenic, erectile dysfunction, and exemplifies use of a sublingual tablet formulation of apomorphine hydrochloride. WO 00/35457 further suggests that nausea, a common side effect of apomorphine, can be controlled by inclusion of an anti-emetic agent such as nicotine in the formulation.

U.S. Patent No. 6,121,276 to El-Rashidy & Ronsen discloses flavored sublingual tablets containing apomorphine hydrochloride and nicotine.

International Patent Publication No. WO 01/49292 discloses sublingual tablets of apomorphine providing prolonged release of the drug, said to be useful in treatment of Parkinson's disease.

International Patent Publication No. WO 00/42992 discloses a dosage unit comprising a water-soluble hydrocolloid and sildenafil citrate in a mucoadhesive film said to be suitable for application to the oral mucosa. Pharmacokinetic data presented in WO 00/42992 indicate no faster absorption into the bloodstream with sublingual application of such a film than with a commercial tablet formulation of sildenafil citrate (Viagra®) at the same dosage.

International Patent Publication No. WO 01/10406 discloses compositions said to be suitable for a wide range of routes of administration of sildenafil citrate, including buccal and sublingual routes. Preferred compositions disclosed are said to comprise a solution, gel, semisolid, suspension, metered dose device, transdermal patch or film.

International Patent Publication No. WO 02/05820 discloses film dosage forms comprising sildenafil citrate. These dosage forms are prepared by mixing a solid dispersion of sildenafil citrate and a water soluble sugar with a hydrocolloid and optionally other ingredients, and are said, upon placement on a mucosal surface, to form a coating that subsequently disintegrates and dissolves to release sildenafil.

International Patent Publication No. WO 02/041840 discloses the use of cocoa powder as a flavorant, though not a taste-masker, in chewing gums for sildenafil citrate.

International Patent Publication No. WO 00/30641 discloses the use of cocoa powder as a flavorant in oral compositions containing nicotine.

International Patent Publication No. WO 99/66916 discloses the use of chocolate flavor in oral compositions containing apomorphine.

Chocolate, which is very different from cocoa powder as such, has very rarely been used as an ingredient in pharmaceutical products on the market, hitherto only in laxatives. One example is Ex-Lax® being chocolated laxative pieces marketed by

Novartis comprising sennosides. Purex, a laxative wherein phenolphthalein was formulated with chocolate, was marketed in the 1950s.

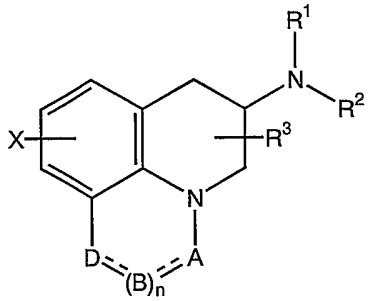
It has now surprisingly been found that a rapid onset of orally administered pharmaceutical compositions of SD compounds is achieved concomitantly with sufficient taste masking of badly tasting ingredients, such as buffering agents, through the use of SD-compound-containing formulations comprising cocoa powder as filler/diluent and taste masking or flavoring agent and agent for providing a smooth texture. No similar formulations have been disclosed hitherto.

Summary of the invention

The present invention provides an orally administered rapid-onset pharmaceutical composition useful for treatment of sexual dysfunction, stimulation of sexual activity and enhancement of sexual desire, interest and performance in men and women. The composition is a dosage form comprising a therapeutically or sexual-stimulatorily effective amount of one or more SD compounds. A "therapeutically effective amount" herein is an amount sufficient to improve sexual desire, interest or performance in a subject having a sexual dysfunction condition. A "sexual-stimulatorily effective amount" herein is an amount sufficient to improve sexual desire, and interest or performance in a subject whether or not the subject has a sexual dysfunction condition.

Suitable such SD compounds are chosen from the below agents, but are not limited thereto:

A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-}

$_6$ alkyl)carbonyl;

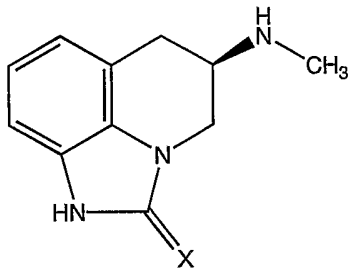
A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

said compound of formula (I) or salt thereof being water-soluble. A suitable dosing is from around 0.1 mg to around 10 mg per dose.

A compound of formula (II)



(II)

wherein X is O or S, and pharmaceutically acceptable salts thereof. A suitable dosing is from around 0.05 mg to around 10 mg per dose.

A compound chosen from phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil in base form and pharmaceutically acceptable salts thereof, including sildenafil citrate marketed under the trademark Viagra®, vardenafil marketed as Nuviva and tadalafil marketed as Cialis®. Suitable dosing is from around 5 mg to around 100 mg per dose.

A compound chosen from dopaminergic agonists, such as apomorphine, with or without addition of anti-emetic agents. Suitable dosing is from 0.5 mg to around 10 mg per dose.

A compound chosen from noradrenergic alpha antagonists or α-adrenergic antagonists, such as phentolamine mesylate marketed as Vasomax, yohimbine and prazosin.

A compound chosen from cyclic AMP activators.

Pharmaceutically acceptable salts, complexes and mixtures of the above compounds are also useful.

It is preferred that the amount of the SD compound, salt, complex or mixture thereof be lower than an amount causing significant side effects.

A particularly useful dosage form of the present invention is a formulation that disintegrates or melts in the mouth without need for drinking water or other fluid.

Preferred dosage forms are tablets, sublingual tablets and lozenges. Chewing gums are not preferred dosage forms.

The invention is adapted for discreet self-administration. By "discreet self-administration" herein is meant self-administration shortly prior to sexual activity in a way that does not draw attention of a sexual partner to, or emphasize, the existence of a sexual dysfunction, a need for therapy or a need or desire for enhancement of sexual performance. The combination of discreetness and rapid onset that is permitted by the present invention provides a benefit in spontaneity; by contrast, prior art compositions for treating sexual dysfunction can be seriously compromised in their effectiveness if their self-administration requires premeditation and/or cannot be done discreetly, such self-administration being thereby not conducive to spontaneity.

Also provided by the present invention are methods of use of compositions of the present invention for treatment of sexual dysfunction and for enhancement of sexual desire, and interest or performance, and a method of use of a composition of the invention for preparing a medicament. Other features of this invention will be in part apparent and in part pointed out hereinafter.

Compositions for the therapeutic delivery of SD compounds are provided. Said compositions comprising SD compounds provide rapid transmucosal absorption in the oral cavity.

The SD compounds of the present invention include the parent forms as well as salts and complexes of the parent forms.

An object of the invention is to provide new pharmaceutical compositions of SD compounds for uptake buccaly or by other mucosa in the oral cavity, especially such compositions comprising a large percentage of cocoa powder.

A second object of the invention is to provide methods for preparing said compositions.

A third object of the invention is methods for using said formulations in sexual dysfunction therapy, including enhancement of sexual desire, and interest or performance.

Further objects of the invention will become apparent to one skilled in the art, and still other objects will become apparent hereinafter from the specification and claims.

The main advantages provided by a composition according to the present invention are:

1) It allows for rapid onset of the pharmacological effect;

2) It provides for good taste masking properties due to the presence of cocoa powder;

3) It does not require any water for swallowing;

4) It provides for possible high bioavailability for substances with high first pass metabolism;

5) It provides for an association of pleasure;

6) It does not give an immediate patient-perceived association with medicines (traditional tablets).

Detailed Description of the Invention

It is the primary object of the present invention to provide rapid-onset pharmaceutical compositions useful for treatment of sexual dysfunction, stimulation of sexual activity and enhancement of sexual desire, interest or performance in men and women. The term "rapid-onset" means that a therapeutic effect is achieved within a short period of time, for example less than about 1 hour, preferably less than 30 minutes, following administration.

More specifically it is the object of the invention to provide such a SD-compound-containing composition, for transmucosal, preferably buccal, delivery, that disintegrates and/or melts at body temperature with or without the aid of salivary fluid or mechanical erosion, or a combination thereof after which the formulation preferably shows adhesiveness towards the tissues in the oral cavity.

The addition of buffering agents provides for a transient change in local pH of the saliva. Thereby a higher fraction of the active agent is transformed into its less ionized form. Thereupon the transmucousal permeation is facilitated, which enhances the absorption of the active agent. For those skilled in the art it is evident that the choice of the buffering system is dependent on the one or more pK_as of the active agent.

It has surprisingly been found that a rapid buccal absorption of SD compounds concomitantly with sufficient taste masking of badly tasting ingredients, such as the active compound and/or buffering agents, is achieved through the use of cocoa powder. The cocoa powder acts as filler/diluent as well as taste masking or flavoring agent and agent for providing a smooth texture. No similar formulations have been disclosed hitherto.

A preferred formulation is a composition, weighing around 400 mg – 500 mg, having the following ingredients:

A therapeutically efficient amount of a SD compound,

cocoa powder around 200 mg,

fatty components around 180 mg,

aspartame around 2.5 mg,

sodium carbonate around 15 mg,

lecithin around 4 mg.

Preferably the composition should comprise at least 15 % by weight of cocoa powder.

Cocoa powder is defined as cocoa nib with some fat removed and ground into a powder. Cocoa nib is defined as cocoa beans with the shell removed. Cocoa butter is defined as fat expelled from the center (kernels or nib) of cocoa beans.

Cocoa powder is prepared from roasted cocoa beans. It is a complex compound, which consists of starch, cocoa butter, amino acids, proteins, xanthines, amines, mono- and polysaccharides, phospholipids, flavonoids, pyrazines, etc.

Preferred fatty components are fats/lipids chosen from tempering fats, including cocoa butter equivalents (CBE) and cocoa butter improvers (CBI), and non-tempering fats, including cocoa butter replacers (CBR) and cocoa butter substitutes (CBS).

According to *Industrial Chocolate Manufacture and Use*, S. T. Beckett, ed., 2nd edition, Blackier Academic & Professional, London, 1994, p 382, chocolate is defined as a product obtained from cocoa nib, cocoa mass powder and sucrose with or without added cocoa butter, having a minimum dry cocoa solids content of 35%, at least 14% of dry non-fat cocoa solids and 18% cocoa butter. Chocolate has two major distinguishing characteristics: its flavor and its texture. A primary feature of the texture is that the chocolate must be solid at a temperature of 20 - 25°C and yet melt rapidly in the mouth at 37°C thereby being transferred to a liquid, which appears smooth to the tongue. The processing of chocolate is related to obtaining these two criteria (*ibid.* p 2).

Neither milk chocolate nor light cooking chocolate or dark cooking chocolate may mask the disagreeable taste of most buffering agents. The cocoa content of milk chocolate is comparatively low (a cocoa mass content of 10 - 16%, corresponding to approximately 5 - 8% cocoa powder). The beans'/cocoa mass' content of dark, bitter-sweet chocolate is 55 - 70% (Beckett, pp. 276 - 277), corresponding to approximately 28 - 35% cocoa powder. By making a vehicle with a high proportion of cocoa powder (30 - 70%) and fatty components (30 -50%), as per the present invention, an effective masking is though obtained. The higher the cocoa powder concentration the better the taste masking.

Examples

Below follows non-limiting examples on preparation of certain embodiments of the present invention.

Example 1: Preparation of a preferred embodiment

A composition, weighing around 400 mg, having the following preferred composition (w/w):

Active:	A SD compound according to above formula (I) in an amount from around 0.25 mg to around 10 mg.
Diluent/filler and flavoring/taste-masking agent and agent for providing a smooth texture:	cocoa powder around 50%
Lipid ingredient:	cocoa butter equivalents (CBE) around 44%
Buffering agent:	sodium carbonate around 4%
Sweetener:	aspartame around 0,6%
Emulsifier/solubilizer:	lecithin around 1%
Flavoring agent:	mint or vanilla flavor 0,5%

is prepared in the following way:

A part of the CBE is melted. The solid components, i e the SD compound, cocoa powder, aspartame, sodium carbonate and the flavoring agent if solid, are added and mixed. A reduction of particle size of the solid components is performed by milling in a roll-refiner. If the solid components have already got the required particle size, e g by milling before the mixing with the fatty components, roll refining is dispensed with. After treatment in the roll-refiner the mixture is mixed with the rest of the melted fatty components or remelted (if solidified) and mixed with the rest of the melted CBE. A mixing of the melt is performed in a suitable mixer. The liquid components, i e lecithin and the flavoring agent if liquid, are added. Tablets or other solid dosage forms are subsequently made using suitable techniques, such as molding, extrusion or congealing, including pastillation, when necessary after suitable preconditioning. Also other suitable manufacturing methods may be used.

Example 2: Preparation of a further embodiment

In essentially the same way as in Example 1 is manufactured a composition with a weight from around 400 mg to around 500 mg having the below ingredients:

from 0.25 mg to around 10 mg thereof of a compound of above formula (II),
around 50% (w/w) cocoa powder,
around 44% (w/w) cocoa butter equivalents (CBE),
around 4% (w/w) sodium carbonate,
around 0,6% (w/w) aspartame and/or acesulfame potassium,
and around 1% (w/w) lecithin.

Example 3: Preparation of a still further embodiment

In essentially the same way as in Example 1 is manufactured a composition with the below contents:

Active:	A SD-compound in a therapeutically sufficient amount.
Diluent/filler and flavoring/taste-masking agent and agent for providing a smooth texture:	Cocoa powder and optionally a small amount of a substance/substances chosen from one or more of the compounds fructose, glucose, galactose, invert sugar, a pharmaceutically acceptable polyol such as xylitol, sorbitol, maltitol, mannitol, isomalt and glycerol, or polydextrose, or any mixture thereof, from around 30% to around 70% (w/w),
Lipid ingredient:	from around 30% to around 50% (w/w),
Buffering agent:	from 0 % to around 10% (w/w),
Sweetener:	from around 0.3% to around 3% (w/w),
Emulsifier/solubilizer:	from around 0.3% to around 5% (w/w),
Flavoring agent:	from 0 % to around 4% (w/w).

Example 4: Preparation of alternative embodiments

Useful embodiments are obtained by exchanging some of the excipients in the embodiments of the above examples for equivalently functioning alternative compounds.

A small part of the cocoa powder may be exchanged for one or more of the compounds fructose, glucose, galactose, lactose, maltose, invert sugar, a pharmaceutically acceptable polyol such as xylitol, sorbitol, maltitol, mannitol, isomalt and glycerol, or polydextrose, or any mixture thereof, but only to such an extent that the taste-masking effect of the cocoa-powder remains sufficient.

The lipid ingredient, being fatty components, may be chosen from one or more of the following compounds:

cocoa butter and cocoa butter alternatives, including cocoa butter equivalents (CBE), cocoa butter substitutes (CBS), cocoa butter replacers (CBR) and cocoa butter improvers (CBI),

- coconut, palmkernel oil and other similar oils characterized by being predominantly based on lauric and myristic acids,

- palm oil, shea butter, karite butter, illipe butter, mango kernel oil, sal fat and other similar fats characterized by being predominantly based on palmitic, oleic and stearic acids,

- corn oil, sunflower oil, hybrid sunflower oil, soybean oil, rapeseed oil, canola oil, olive oil, ricebran oil, cottonseed oil, arachis (peanut, groundnut) oil and other oils characterized by being predominantly based on oleic, linoleic and linolenic acids and hydrogenated to a suitable melting point,

- fish oil, tallow, lard, butterfat and other animal derived fats, and

- synthetic fats, reesterified fats, hard fats obtained by a chemical reaction of fatty acids with glycerol using no, acidic, alkaline or enzymatic catalysis,

whereby said compound(s) is/are used as a single component or mixed with each other, being either crude or refined using physical or alkaline refining, or being subjected to further processing including catalytic hydrogenation, interesterification, transesterification and fractionation.

The buffer sodium carbonate may be exchanged for carbonates, bicarbonates, acetates, gluconates, glycerophosphates, phosphates or glycinates of sodium, potassium or ammonium, or mixtures thereof. Most phosphates are though less suitable because their taste usually is disagreeable and difficult to mask.

The sweetener aspartame may entirely or in part be exchanged for one or more other artificial sweeteners, such as acesulfame potassium, saccharine, sodium saccharine, cyclamate and glycyrrhizine and/or salts thereof.

The emulsifier lecithin is preferably soy lecithin and/or egg lecithin, but may be exchanged for

- a nonionic surfactant, such as poloxamer, polyoxyethylene alkyl ether, polyoxyethylene castor oil derivative, polyoxyethylene sorbitan fatty acid ester, monoglyceride, diglyceride and esther thereof, polyoxyethylene stearate, polyglycerolester of fatty acids (including polyglycerolpolyricinoleic acid (PGPR)), sorbitan fatty acid ester,

- an anionic surfactant, such as fatty acid, soap of fatty acid, lactylate, especially sodium and/or calcium stearoyllactylate, sodium lauryl sulfate and latanol,

- a zwitterionic surfactant, such as zwitterionic phospholipid, such as phosphatidylcholine and phosphatidylethanolamine,

or mixtures, fractions or derivatives thereof or with lecithin.

In principally the same way as in the above examples compositions comprising other SD compounds may be manufactured. The dose range and the percentages of the excipients should in such cases be accordingly adjusted.

CLAIMS

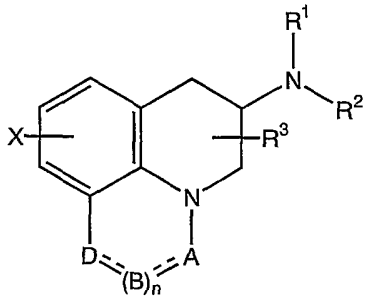
1. A sexual-dysfunction-compound-containing orally administered rapid-onset pharmaceutical composition, c h a r a c t e r i z e d in that it comprises cocoa powder.

2. A composition according to claim 1, c h a r a c t e r i z e d in that it comprises at least 15% cocoa powder.

3. A composition according to claim 1 or 2, c h a r a c t e r i z e d in that it further comprises one or more lipid ingredients.

4. A composition according to any preceding claim, c h a r a c t e r i z e d in that the sexual-dysfunction-compound/s is/are chosen among the following compounds

a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

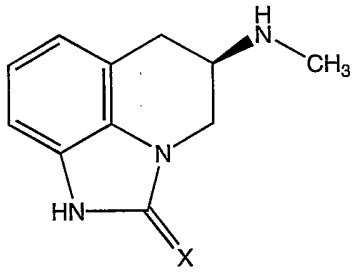
A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

said compound of formula (I) or salt thereof being water-soluble;

a compound of formula (II)



(II)

wherein X is O or S, and pharmaceutically acceptable salts thereof;

a compound chosen from phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil in base form and pharmaceutically acceptable salts thereof, including sildenafil citrate, vardenafil and tadalafil;

a compound chosen from dopaminergic agonists, such as apomorphine optionally with the addition of anti-emetic agents;

a compound chosen from noradrenergic alpha antagonists or α-adrenergic antagonists, such as phentolamine mesylate, yohimbine and prazosin;

a compound chosen from cyclic AMP activators;

and pharmaceutically acceptable salts, complexes and mixtures thereof.

5. A composition according to any of claims 1-4, c h a r a c t e r i z e d in that it further comprises one or more buffering agents.

6. A composition according to claim 5, c h a r a c t e r i z e d in that the one or more buffering agents is/are chosen from carbonates, bicarbonates, acetates, gluconates, glycerophosphates, phosphates or glycinates of sodium, potassium or ammonium, or mixtures thereof.

7. A composition according to any preceding claim, c h a r a c t e r i z e d in that it further comprises one or more sweeteners and optionally one or more flavoring agents.

8. A composition according to claim 7, c h a r a c t e r i z e d in that the one or more sweeteners is/are aspartame, acesulfame potassium, saccharine, sodium saccharine, cyclamate and/or glycyrrhizine and/or salts thereof.

9. A composition according to any of claims 3-8, c h a r a c t e r i z e d in that the one or more lipid ingredients is/are chosen from

- cocoa butter and cocoa butter alternatives, including cocoa butter equivalents (CBE), cocoa butter substitutes (CBS), cocoa butter replacers (CBR) and cocoa butter improvers (CBI),

- coconut, palmkernel oil and other similar oils characterized by being predominantly based on lauric and myristic acids,

- palm oil, shea butter, karite butter, illipe butter, mango kernel oil, sal fat and other similar fats characterized by being predominantly based on palmitic, oleic and stearic acids,

- corn oil, sunflower oil, hybrid sunflower oil, soybean oil, rapeseed oil, canola oil, olive oil, ricebran oil, cottonseed oil, arachis (peanut, groundnut) oil and other oils characterized by being predominantly based on oleic, linoleic and linolenic acids and hydrogenated to a suitable melting point,

- fish oil, tallow, lard, butterfat and other animal derived fats, and

- synthetic fats, reesterified fats, hard fats obtained by a chemical reaction of fatty acids with glycerol using no, acidic, alkaline or enzymatic catalysis,

whereby said compound(s) is/are used as a single component or mixed with each other, being either crude or refined using physical or alkaline refining, or being subjected to further processing including catalytic hydrogenation, interesterification, transesterification and fractionation.

10. A composition according to claim 9, c h a r a c t e r i z e d in that the one or more lipid ingredients is/are chosen from cocoa butter equivalents (CBE), cocoa butter substitutes (CBS) and cocoa butter replacers (CBR).

11. A composition according to any preceding claim, c h a r a c t e r i z e d in that it further comprises one or more emulsifiers/solubilisers.

12. A composition according to claim 11, c h a r a c t e r i z e d in that the one or more emulsifiers/solubilisers is/are chosen from

- lecithin, preferably soy lecithin and/or egg lecithin,

- a nonionic surfactant, such as poloxamer, polyoxyethylene alkyl ether, polyoxyethylene castor oil derivative, polyoxyethylene sorbitan fatty acid ester, monoglyceride, diglyceride and esther thereof, polyoxyethylene stearate, polyglycerolester of fatty acids (including polyglycerolpolyricinoleic acid (PGPR)), sorbitan fatty acid ester,

- an anionic surfactant, such as fatty acid, soap of fatty acid, lactylate, especially sodium and/or calcium stearoyllactylate, sodium lauryl sulfate and latanol,

- a zwitterionic surfactant, such as zwitterionic phospholipid, such as phosphatidylcholine and phosphatidylethanolamine,

or mixtures, fractions or derivatives thereof or with lecithin.

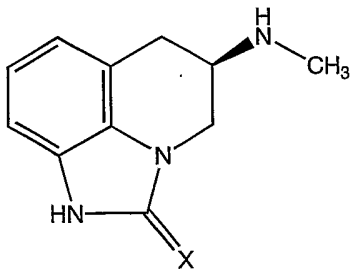
13. A composition according to claim 12, c h a r a c t e r i z e d in that the one or more emulsifiers/solubilisers is/are chosen from lecithin, preferably soy lecithin and/or egg lecithin.

14. A composition according to any preceding claim, c h a r a c t e r i z e d in that it further comprises a small amount of a substance/substances chosen from one or more of the compounds fructose, glucose, galactose, lactose, maltose, invert sugar, a pharmaceutically acceptable polyol such as xylitol, sorbitol, maltitol, mannitol, isomalt and glycerol, or polydextrose, or any mixture thereof.

15. A sexual-dysfunction-compound-containing orally administered rapid-onset pharmaceutical composition, c h a r a c t e r i z e d in that a unit dose thereof comprises

Active:	A sexual-dysfunction-compound in a therapeutically sufficient amount,
Diluent/filler and flavoring/taste-masking agent and agent for providing a smooth texture:	Cocoa powder and optionally a small amount of a substance/substances chosen from one or more of the compounds fructose, glucose, galactose, invert sugar, a pharmaceutically acceptable polyol such as xylitol, sorbitol, maltitol, mannitol, isomalt and glycerol, or polydextrose, or any mixture thereof, from around 30% to around 70% (w/w),
Lipid ingredient:	from around 30% to around 50% (w/w),
Buffering agent:	from 0% to around 10% (w/w),
Sweetener:	from around 0.3% to around 3% (w/w),
Emulsifier/solubilizer:	from around 0.3% to around 5% (w/w),
Flavoring agent:	from 0% to around 4% (w/w).

16. A sexual-dysfunction-compound-containing orally administered rapid-onset pharmaceutical composition, c h a r a c t e r i z e d in that a unit dose thereof comprises from 0.25 mg to around 10 mg thereof of a compound of formula (II)



(II)

wherein X is O or S, and pharmaceutically acceptable salts thereof,

around 50% (w/w) cocoa powder,

around 44% (w/w) cocoa butter equivalents (CBE),

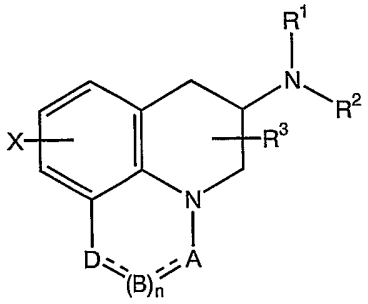
around 4% (w/w) sodium carbonate,

around 0,6% (w/w) aspartame and/or acesulfame potassium,

and around 1% (w/w) lecithin.

17. A sexual-dysfunction-compound-containing orally administered rapid-onset pharmaceutical composition, c h a r a c t e r i z e d in that a unit dose thereof comprises

Active: A sexual-dysfunction compound according to formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

in an amount from around 0.25 mg to around 10 mg.

Diluent/filler and flavoring/taste-masking agent and agent for providing a smooth

texture:	cocoa powder around 50%
Lipid ingredient:	cocoa butter equivalents (CBE) around 44%
Buffering agent:	sodium carbonate around 4%
Sweetener:	aspartame around 0,6%
Emulsifier/solubilizer:	lecithin around 1%
Flavoring agent:	mint or vanilla flavor 0,5%

18. A composition according to any preceding claim, which is formulated as an oral dosage form and which provides for delivery of sexual-dysfunction-compounds through the buccal mucosa and/or other mucosa of the oral cavity.

19. A composition according to any preceding claim, which is formulated as a tablet, as a sublingual tablet or as a lozenge.

20. A composition according to any of claims 1–18, which is formulated as an oral dosage form not being a chewing gum.

21. Use of a composition according to any preceding claim for the manufacture of a medicament useful for treatment of sexual dysfunction, stimulation of sexual activity and enhancement of sexual desire and interest or performance.

22. Method for treating sexual dysfunction in a subject comprising administration of a sexual-dysfunction-compound-containing rapid-onset orally administered pharmaceutical composition according to anyone of claims 1–18 to the subject.

23. Method according to claim 22 comprising administration of a sexual-dysfunction-compound-containing rapid-onset orally administered pharmaceutical composition according to anyone of claims 1–20 to the subject less than 1 hour, preferably less than 30 minutes prior to sexual activity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/00, A61K 31/435, A61K 31/505, A61K 31/4745, A61K 31/437, A61K 47/46, A61P 15/00

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)

IPC7: A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02074321 A1 (N.V. NUTRICIA), 26 Sept 2002 (26.09.02), the claims, page 10, line 15 - page 14, line 16	1-23
P,X	WO 02062315 A1 (PHARMACIA CORPORATION), 15 August 2002 (15.08.02), the claims, page 7, line 16	1-23
X	WO 0241840 A2 (WM. WRIGLEY JR. COMPANY), 30 May 2002 (30.05.02), page 15, line 28 - page 16, line 15, claims 1-8	1-23

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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
29 August 2003	02 -09- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01022

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.: 22, 23
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
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:

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 searched 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01022

Claims 22-23 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0205820 A1 (LAVIPHARM LABORATORIES, INC.), 24 January 2002 (24.01.02), page 11, 5th paragraph, the claims	1-23
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X	WO 9966916 A1 (PENTECH PHARMACEUTICALS, INC.), 29 December 1999 (29.12.99), page 12 - page 13, page 49, page 51, page 53, the claims	1-23
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A	FR 2717387 A1 (HI PHARMTECH), 22 Sept 1995 (22.09.95)	1-23
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A	STN International, File CAPLUS, CAPLUS accession no. 2002:513067, Document no. 137:68208, Meiji Seika Kaisha, Ltd.: "Cocoa powder-containing pharmaceutical formulations"; & JP,A2,2002193839, 20020710	1-23
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A	File EPODOC/EPO, LVATSA LAB SA(ES): "Oral pharmaceutical composition of ciprofloxacin, non-aqueous, stable and with improved organoleptic characteristics", ES,A,2105970, 19971016	1-23
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A	WO 0030641 A1 (PHARMACIA & UPJOHN AB), 2 June 2000 (02.06.00), the claims, page 10, line 7 - line 18	1-23
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A	WO 0040226 A2 (PHARMACIA & UPJOHN COMPANY), 13 July 2000 (13.07.00), page 14, line 1 - line 10, page 14, line 22 - page 15, line 15, claims 1-21	1-23
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A	WO 9830209 A1 (PFIZER PHARMACEUTICALS INC.), 16 July 1998 (16.07.98), the examples, the claims	1-23
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CAPLUS, CAPLUS accession no. 2000:271985, Document no. 132:284269, Eisai Co., Ltd.: "Oral formulations containing cGMP phosphodiesterase inhibitors and anionic polymers"; JP,A2,2000119198, 20000425 --	1-23
A	EP 0960621 A2 (PFIZER INC.), 1 December 1999 (01.12.99), column 1, line 40 - column 2, line 38 -- --------	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

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WO 02062315 A1	15/08/02	US 2003022912 A	30/01/03
WO 0241840 A2	30/05/02	AU 3656602 A	03/06/02
		US 6531114 B	11/03/03
		US 2002012633 A	31/01/02
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01022

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		BG 103396 A	31/01/00
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		JP 11353357 A	24/12/99
		NO 992339 A	16/11/99
		NZ 335772 A	22/12/00
		PL 333118 A	22/11/99
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