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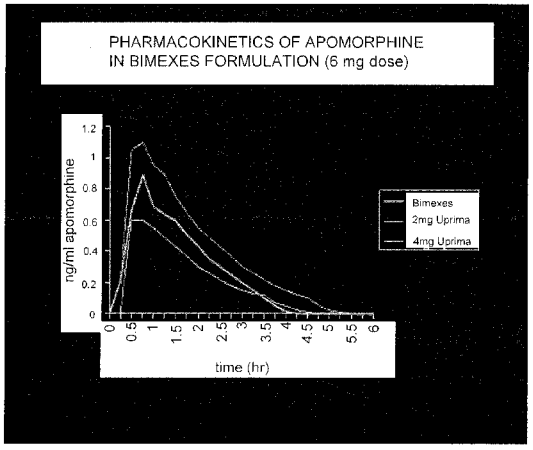
(54) Title: COMBINATION THERAPY FOR TREATING FEMALE HYPOACTIVE SEXUAL DESIRE DISORDERS

Figure 1



(57) Abstract: Improved compositions and methods for modulating the female human sexual response in the treatment of hypoactive sexual desire disorder are presented, comprising a combination of an alpha-adrenergic antagonist and a norepinephrine and dopamine reuptake inhibitor and/or dopaminergic agonist. The combination produces a synergistic increase in female erectile response with simultaneous increase in libido, to provide on demand therapeutic treatment of female hypoactive sexual desire disorder.

COMBINATION THERAPY FOR TREATING FEMALE HYPOACTIVE SEXUAL DESIRE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/265,897 filed December 10, 2015, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The application is directed to the compositions and methods useful in modulating the human female sexual response on demand.

BACKGROUND OF THE INVENTION

[0003] The human sexual response in both males and females results from a complex interplay of psychological, hormonal, and other physiological influences. One important aspect of human sexual response that is common to both men and women is the erectile response which itself results from the interplay between the autonomic nervous system, the endocrine system, and the circulatory system. Failure of the erectile response in both men and women results in impotence. Although male erectile dysfunction has generated a great deal of research resulting in the discovery and development of a number of drugs and methods for alleviating male impotence, similar progress in modulating the female erectile response has garnered much less attention. In addition to the erectile response, required to achieve potency, the human sexual response also depends on issues of libido, the desire to engage in sexual activity. Recent research suggests that libido may play a significantly greater role in the female sexual response than in males. Female hypoactive sexual desire disorders (HSDD) afflict approximately 40% of women and there are few treatment options. HSDD is more prevalent in older women and is a progressive and widespread condition. Common symptoms include lack of vaginal dilation, lubrication or tumescence, little interest in or thoughts of sex and little pleasure in sex. HSDD is generally considered to encompass elements of both sexual arousal disorder and sexual desire disorder, illustrating the degree to which potency and libido are intertwined in the female human sexual response. An effective therapy for HSDD must be capable of modulating both potency and libido to be effective.

[0004] Presently, the most popular method of treating male erectile disorders involves administering sildenafil (Viagra®); however sildenafil is of limited efficacy in women. In women, sildenafil works by decreasing cyclic guanosine monophosphate metabolism, resulting in nitric oxide-mediated vasodilation and relaxation of the vaginal smooth muscles and clitoris. *See* Barna, et al., *Female Sexual Dysfunction: from causality to cure.* U.S. Pharmacist 33(11): epub (2008). Clinical trials of pre- and post-menopausal women produce conflicting results regarding the efficacy of sildenafil on the overall female human sexual response, with younger women experiencing improvements in both potency and libido and older women experiencing little improvement in satisfaction and overall sexual function. *See* Caruso, et al., *Premenopausal women affected by sexual arousal disorder treated with sildenafil: a double-blind cross-over, placebo-controlled trial.* British Journal of Gynaecology 108:623 (2001) *and* Kaplan, et al., *Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction.* Urology 53:481 (1999). The difference in response of younger and older women to sildenafil further underscores the complexity of the interplay between the various factors determining potency and libido in human females. Whereas with men, simply restoring potency is generally enough to provoke desire (libido), this does not appear to be the case with women, especially with post-menopausal women.

[0005] Libido is frequently correlated with levels of serum testosterone, which may account for the observed differences in effectiveness of sildenafil in younger and older women. Indeed, hormone replacement therapy involving administration of exogenous estrogen, which serves to raise testosterone in post-menopausal women, is often recommended, in part, to alleviate the symptoms of HSDD. Treatment of women suffering low libido with testosterone, alone or in combination with other drugs, has resulted in mixed success in restoring libido. For example, LibiGel® (BioSante Biopharmaceuticals), a low dose (300 microgram) gel formulation of topical testosterone recently completed Phase 3 trials but failed to demonstrate efficacy in increasing the total number of days with a satisfying sexual event from baseline or an increase in mean sexual desire from baseline. An intranasal low-dose formulation of testosterone, TBS-2 (Trimel Biopharma SRL) has completed Phase 2 trials in the United States, but the resulting number of satisfying sexual events over the trial period

has not been made available. Combination drugs, such as Lybrido (Emotional Brain NY, Inc.), which is a combination of testosterone and sildenofil, and Lybridos (Emotional Brain NY, Inc.), a combination of testosterone and buspirone (a 5HT1A receptor antagonist that also binds dopamine type 2 receptors) are also available, but have had only limited success in treating female hypoactive sexual desire disorder. More recently, flibanserin (Addyi®, Sprout Pharmaceuticals, Inc.), another compound with affinity for 5HT1A and 5HT2 receptors was approved as an oral treatment for women suffering from hypoactive sexual desire disorder and has proven effective in increasing libido.

SUMMARY OF THE INVENTION

[0006] The present invention provides improved compositions and methods for modulating the female human sexual response by administering two or more pharmaceutically active agents to the circulation, the combination of which results in improved sexual responsiveness, for example, by improving blood flow to the genitalia by various physiological mechanisms. In one embodiment of the invention, the female human sexual response is modulated on demand by the administration of an effective response modulating amount of two or more pharmaceutically active agents one of which is an alpha-adrenergic antagonist and the other a dopaminergic agonist, together in an orally administrable formulation. Preferably, the formulation comprises the pharmaceutically active agents in an orally administrable tablet.

[0007] Another aspect of the present invention is directed to a combination of a first pharmaceutically active agent and a second pharmaceutically active agent wherein the first pharmaceutically active agent is an alpha-adrenergic antagonist selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, or any pharmaceutically acceptable salt thereof, and wherein the second pharmaceutically active agent is a dopaminergic agonist selected from the group consisting of buspirone, flibanserin or apomorphine. A preferred first pharmaceutically active agent is phentolamine mesylate. A preferred dopaminergic agonist useful in the practice of the invention is apomorphine in any of its

pharmaceutically useful forms, including but not limited to apomorphine hydrochloride.

[0008] The invention also contemplates formulations comprising an alpha-adrenergic antagonist such as phentolamine mesylate in combination with an agent which activates 5-HT1A receptors in a human subject to disinhibit norepinephrine and dopamine release. In yet another of the embodiments of the present invention, two or more pharmaceutically active agents may be separately administered so long as the two or more agents are present in the circulation simultaneously so as to exert their combined effects.

[0009] A preferred oral formulation comprises in combination, at least a first and a second pharmaceutically active agent in a rapidly dissolving orally administrable tablet. Preferred rapidly dissolving tablets have disintegration times from about 1 minute to about 10 minutes. Most preferred are rapidly dissolving tablets having the disintegration times of less than one minute. Preferred oral doses of phentolamine mesylate in the formulations of the present invention are preferably from about 5 mg to about 100 mg. Preferred oral doses of apomorphine in the same tablet are preferably from about 5 mg to about 50 mg.

[0010] Previously, a combination of phentolamine and apomorphine has been used described for treating erectile dysfunction in males (Place, et al., *Dosage and inserter for treatment of erectile dysfunction.* U.S. Patent No. 5,474,535 (the '535 patent)). However, the '535 patent involves treatment in which the active agents are directly administered to the urethra by means of a mechanical device inserted into the penis. Obviously, such administration would not be effective for treatment of females suffering from hypoactive sexual desire disorder.

[0011] Apomorphine has been described as effective in improving the sexual experience of women suffering from hypoactive sexual desire disorder. However, best results were obtained when apomorphine was administered (sub-lingual) on a daily basis (2-3 mg/daily). Under this regimen 20 of 37 women completing the two week trial period reported improvements in sexual satisfaction. In contrast, only 6 of

55 women receiving apomorphine (2-3 mg sub-lingual) on an "as needed" or "on demand" basis prior to sexual activity reported any improvement in sexual satisfaction. Thus, although apomorphine appears to be effective in treating some aspects of female hypoactive sexual desire disorder it requires daily administration. *See* Caruso et al., *Placebo-Controlled Study on Efficacy and Safety of Daily Apomorphine SL intake in Premenopausal Women Affected by Hypoactive Sexual Desire Disorder and Sexual Arousal Disorder.* Urology 63:955 (2004). Recently, flibanserin has received approval for use in treating female hypoactive sexual desire disorder. Administration of flibanserin is on a daily basis, and as with sub-lingual administration of apomorphine, does not appear to be effective as an "on demand" therapy. *See* Borsini and Evans, *Treating Sexual Desire Disorder with Flibanserin.* U.S. Patent Application No. 8,227,471. The present invention is directed to methods for improving the sexual response in women (i.e., excitation, plateau, and orgasmic phases of the female sexual response) on demand by oral administration of an effective amount of the compositions of the present invention.

[0012] The methods and compositions of the present invention are also useful in preparation for sexual intercourse by virtue of their ability to improve the sexual response in females in less than one hour after administration. To be effective, the therapeutic treatment must minimize side effects associated with alpha-adrenergic antagonists and dopaminergic agonists. For example, alpha- andrenergic antagonists such as phentolamine mesylate can cause rhinitis, headache and tachycardia. Likewise, dopaminergic agonists such as apomorphine can induce headache, dizziness, hypotension, nausea and vomiting. Obviously, such side effects are inimical to use of such agents as an "on demand" therapy for enhancing the female sexual response. Unless such therapeutics can be delivered in a manner and mode which avoids such side-effects these therapeutic cannot be used to effectively treat female hypoactive sexual desire disorder. An important aspect of the present invention is that the claimed dosages represent the levels at which the combination of alpha-adrenergic antagonists and dopaminergic agonists have maximum effect on the female sexual response with minimal side effects, thus identifying the critical point of maximal therapeutic effect.

[0013] The present invention is also directed to the use of at least a first and a second pharmaceutically active agent, or a combination of pharmaceutically active agents or any of their pharmaceutically accepted salts, one of which potentiates the sexual response improving ability of one or more of the other agents. The pharmaceutically active agents may, in combination, be used for the manufacture of a medicament for oral administration to a human subject to improve, on demand, the sexual response and, more particularly, to improve response to sexual stimulation.

[0014] The present invention is also directed to the use of at least a first and a second pharmaceutically active agent, or a combination of pharmaceutically active agents, one of which potentiates the sexual response improving ability of one or more of the other agents. The pharmaceutically active agents may, in combination, be used for the manufacture of a medicament for oral administration to a female to improve, on demand, the sexual response and, more particularly, to improve response to sexual stimulation.

[0015] First pharmaceutically active agents useful for manufacturing the medicament include, but are not limited to alpha-adrenergic antagonists. More particularly, the pharmaceutically active agents include phentolamine mesylate, and phentolamine hydrochloride.

[0016] Second pharmaceutically active agents useful for manufacturing the medicament include, but are not limited to norepinephrine and dopamine reuptake inhibitors and dopaminergic agonists. More particularly, the pharmaceutically active agents include buspirone, flibanserin and apomorphine.

[0017] It is also recognized that any of the pharmaceutically active agents useful in the practice of the invention may be used as a free base, pharmaceutically acceptable salts, hydrates, and other forms such as described with respect to phentolamine.

[0018] Numerous other advantages of the present invention will be apparent from the following detailed description of the invention including the accompanying examples and the appended claims.

DESCRIPTION OF THE DRAWINGS

[0019] **Figure 1** illustrates the pharmacokinetic time course of apomorphine present in serum of human subjects administered apomorphine (2 mg and 4 mg doses) and a combination of phentolamine (40 mg) and apomorphine (6 mg). While the maximum peak of circulating apomorphine occurs at about the same time (30-45 minutes after administration) in each example, the overall amplitude of the 6 mg apomorphine administered in combination with phentolamine is less than that of the 4 mg dose of apomorphine administered alone. Also, the time required to clear apomorphine administered in conjunction with phentolamine is less than that required to clear even a 2 mg dose of apomorphine delivered alone.

[0020] **Figure 2** depicts the range of circulating apomorphine measured in serum of human subjects administered with apomorphine (2 mg and 4 mg doses) and a combination of phentolamine (40 mg) and apomorphine (6 mg). The data indicate that in the presence of phentolamine the observed range of circulating apomorphine is proportionally much narrower than that observed in subjects in which apomorphine is administered alone.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention encompasses a combination of an alpha-andrenergic inhibitor, such as phentolamine mesylate, and a dopaminergic agonist, such as apomorphine, in an "on demand" formulation that can be orally administered prior to sexual activity to overcome symptoms of female hypoactive desire disorder. Such combination represents an improvement over existing treatments which require continuous dosing to maintain therapeutic levels of active ingredient, or administration in such a way that significant first pass metabolism can degrade the active ingredient, thereby reducing effectiveness and increasing the side effects associated with the metabolic break down products of the active ingredient.

[0022] To avoid first pass metabolism of the active ingredients of the invention, a sufficient bolus of drug must be delivered to drive absorption by the target tissues based on concentration gradient. This requires rapid release of the active compounds

to achieve therapeutic concentrations as quickly as possible without exceeding safe levels of exposure. Current technologies for delivering the active ingredients of the invention are limited to methods involving regular or delayed release. For example, oral administration of flibanserin or sub-lingual administration of apomorphine are both understood to be effective in the treatment of female hypoactive sexual desire disorder, but require daily dosing. In contrast, the present invention involves a quick release tablet or capsule containing rapidly dispersed therapeutic compositions that are effective on an on demand basis.

[0023] One requirement of on demand dosing is that the therapeutic compounds reach an effective concentration in the body as rapidly as possible. Preferably within approximately one hour. Figure 1 depicts the time course of apomorphine detected in the blood after administration of rapid release tablet containing 40 mg of phentolamine and 6 mg apomorphine, as described in Example 1, to a human subject. The serum level of apomorphine rises rapidly and reaches a maximal level at approximately 30-45 minutes after administration and then declines gradually as the active compound is metabolized. Complete washout required approximately 4 hours. This is similar to the serum profile exhibited by phentolamine (see Table 8 of Lowery, *Methods and Formulations for Modulating the Human Sexual Response*. U.S. Patent No. 5,731,339) which also peaks at about 30-45 minutes and is cleared from the body in about 4 hours. Interestingly, the peak level of apomorphine produced by a 6 mg dose in combination with 40 mg of phentolamine is intermediate to that of 2 mg and 4 mg doses of apomorphine administered without phentolamine and the time to clearance appears to be substantially reduced as well. This indicates that the combination of phentolamine and apomorphine controls the circulating level of apomorphine and enhances clearance of the drug.

[0024] Another requirement of on demand dosing is that the therapeutic compounds do not exceed safe levels within the body. Figure 2 illustrates the range of serum apomorphine observed in human subjects upon administration of apomorphine with and without co-administration of phentolamine. Unexpectedly, in both cases in which apomorphine was administered without co-administration of phentolamine the concentration range varied to a much greater degree than when apomorphine and

phentolamine were co-administered. Consistent with the time course data, the average amount of apomorphine detected in serum was lower from 6 mg apomorphine in combination with 40 mg phentolamine than in serum from subjects administered 4 mg of apomorphine without concomitant administration of phentolamine. This further indicates that co-administration of phentolamine and apomorphine serves to regulate the availability of apomorphine in the blood stream to desired therapeutic levels.

[0025] Co-administration of an alpha-adrenergic antagonist such as phentolamine mesylate and a dopaminergic agonist such as apomorphine produces a rapid increase in the concentration of the dopaminergic agonist within a limited concentration range and facilitates washout of the compound over a shorter period of time than administration of the dopaminergic compound alone. This profile is ideal for use in treatment of female human sexual desire disorder in that it provides limited, but effective dosing on demand.

[0026] The following Examples are among the preferred embodiments of the invention.

Example 1

Rapidly Dissolving Formulations for the Oral Administration of Agents to Modulate Female Potency and Libido

[0027] One aspect of the present invention is directed to rapidly dissolving orally administered compositions for the rapid delivery of pharmaceutically active agents to the systemic circulation thereby allowing a rapid (on demand) onset of improved female erectile response to sexual stimulation. Preferably, the composition comprises a combination of two or more pharmaceutically active agents. Preferably one of the two or more agents is an alpha-adrenergic antagonist and the other is a norepinephrine and dopamine reuptake inhibitors and/or a dopaminergic agonist. The invention is also directed to other orally administered formulations for "on demand" improvement in female erectile response to sexual stimulation including chewable tablets, effervescent formulations, wafers, chewing gum, solutions, lozenges, troches, powders, solutions, suspensions, emulsions, or encapsulated powders or encapsulated

crystals which capsule can be of the gelatin type or other types. As is clear from the foregoing, the compositions may be administered by other than the oral route although the oral route is preferred. The composition may be administered topically, transmucosally, transdermally, and by other methods via other drug delivery media. Other drug delivery media may also be used to administer the compositions of the invention including suppositories (rectal or vaginal), creams, gels, or other drug delivery media well known in the art.

[0028] Exemplary formulations of a rapidly dissolving tablet that includes the alpha-adrenergic antagonist phentolamine mesylate and the dopaminergic agonist apomorphine are set out below.

Table 1:

component	mg/tablet
Phentolamine Mesylate, USP	40
Apomorphine	6
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	184
Microcrystalline Cellulose, NF	142
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

[0029] The ingredients set out in Table 1 (and those used tablet formulations set out below) are finely divided and mixed thoroughly before being compression formed into tablets having a total weight of about 400 mg. Other methods of mixing and tablet formation will be readily apparent to those of skill in the art. Physical characteristics of the tablet prepared by this method include an average hardness of 10.7 Kp, an average thickness of about 0.20 inches and an average disintegration time of about 0.71 minutes.

[0030] As shown in Table 1, the disintegrant, croscarmellose sodium NF (available as Ac-Di-Sol®, from FMC Corporation) was used to accelerate the dissolution of the

tablet although other disintegrants such as those described below may be used to achieve the same effect.

[0031] Tablets useful in the practice of the present invention may include other pharmaceutical excipients, pharmaceutically acceptable salts, carriers, and other substances well known in the art. Buffering agents, flavoring agents, and inert fillers such as lactose, sucrose, corn starch, binders such as acacia, cornstarch, or gelatin. Disintegrants such as potato starch and analgetic acid as well as other commercially available disintegrants including Explotab® sodium starch glycolate, Polyplasdone XL® crospovidone NF, Starch 1500® pregelatinized starch NF. Gissinger et al., *A Comparative Evaluation of the Properties of Some Tablet Disintegrants*, Drug Development and Industrial Pharmacy 6(5):511-536 (1980) also describes other disintegrants and methods for measuring disintegration time of tablets and is incorporated herein by reference. A method for measuring disintegration times of tablets is also set out in European Pharmacopeia 1980 and the U.S. Pharmacopeia which are also incorporated herein by reference. Preferred disintegration times for the practice of the present invention are less than about 20 minutes. More preferred are disintegration times of two minutes or less. Most preferred is a dissolution time of less than one minute. Preferred dissolution times may vary depending on the pharmacokinetic properties of the vasodilator agent itself.

[0032] Formulations useful in the practice of the present invention may vary so long as the formulation maintains the properties of rapid dissolution and improved bioavailability of the active ingredient or ingredients.

[0033] Another example of a rapidly disintegrating tablet formulation is described in Pebley, et al., *Rapidly disintegrating tablet*. U.S. Pat. No. 5,298,261 (the '261 patent) which is incorporated herein by reference. The '261 patent describes a rapidly dissolving tablet comprising a drug and a matrix network that has been vacuum-dried below the equilibrium freezing point of the matrix but above its collapse temperature. The matrix network set out in the '261 patent preferably includes a gum, a carbohydrate, and the drug. Preferred gums include acacia, guar, xanthine, carrageenan, or tragacanth. Preferred carbohydrates described in the '261 patent

include mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, or corn syrup solids.

[0034] Another rapidly dissolving drug carrier is described in Ecanow, *Freeze dry composition and method for oral administration of drugs, biologicals, nutrients and foodstuffs*. U.S. Pat. No. 5,079,018 (the '018 patent) which is incorporated herein by reference. The '018 patent describes a readily dissolvable carrier that comprises a drug, an interim skeletal structure of a water soluble, hydratable gel or foam forming material, preferably a proteinaceous material..

[0035] Other illustrative formulations are set out below.

Table 2:

component	mg/tablet
Phentolamine Mesylate, USP	20
Apomorphine	6
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	194
Microcrystalline Cellulose, NF	152
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

Table 3:

component	mg/tablet
Phentolamine Mesylate, USP	60
Apomorphine	6
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	174
Microcrystalline Cellulose, NF	132
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

[0036] Alternate rapid release formulations suitable for on demand treatment of female hypoactive sexual desire disorder may comprise different norepinephrine and dopamine reuptake inhibitors and dopaminergic agonists. Compounds such as busprione and flibanserin may be incorporated into the formulations as depicted in Tables 4 and 5, respectively. The dose of such alternate norepinephrine and dopamine reuptake inhibitors and dopaminergic agonists may be adjusted to optimize the effectiveness of combining the drug with an alpha-adrenogeric antagonist such as phentolamine.

Table 4:

component	mg/tablet
Phentolamine Mesylate, USP	40
Buspirone	20
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	170
Microcrystalline Cellulose, NF	142
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

Table 5:

component	mg/tablet
Phentolamine Mesylate, USP	40
Flibanserin	100
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	110
Microcrystalline Cellulose, NF	122
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

[0037] After mixing of the ingredients, tablets are prepared by direct compression. Physical characteristics of the tablets prepared according to Tables 2 and 3 are very similar to those described for tablets prepared according to Table 1.

[0038] It is recognized that the norepinephrine and dopamine reuptake inhibitors and/or dopaminergic agonists contemplated by the invention may have bioavailability characteristics that differ from phentolamine mesylate. However, the foregoing information identified particular characteristics useful in optimizing the certain orally administrable formulations of the invention.

[0039] While the studies described above were conducted using a rapidly dissolving formulation (as a preferred embodiment), other formulations that allow rapid absorption of the combination of active agents and corresponding improvement in female sexual response are within the scope of the present invention. For example, the present invention also includes a chewable tablet formulation shown in Table 6.

Table 6:

component	mg/tablet
Phentolamine Mesylate, USP	40
Apomorphine	6
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	120
Sweetrex	258
Aspartame	16
ProSweet	8
Peppermint Flavor #860-172	40
Total Tablet Weight	500

[0040] A number of pharmaceutically active agents may be used in the compositions according to the practice of the present invention based on their demonstrated efficacy as norepinephrine and dopamine reuptake inhibitors and/or dopaminergic agonists. Useful drugs include those generally classified as alpha-adrenergic antagonist, norepinephrine and dopamine reuptake inhibitors,

dopaminergic agonists, and those agents which exhibit direct relaxation of vascular smooth muscle.

[0041] As discussed above, exemplary alpha-adrenergic antagonists useful in the compositions of the present invention include phentolamine hydrochloride and phentolamine mesylate. Phentolamine mesylate is preferred in the practice of the present invention.

[0042] A preferred dopaminergic agonist useful in the compositions of the invention is apomorphine.

[0043] In one aspect the practice of the present invention, these pharmaceutically active agents are administered in rapidly dissolving orally administered formulation or other formulations such as troches, lozenges, chewable tablets, effervescent formulation, powders, solutions, and other formulations that provide for rapid delivery of the active agent to the systemic circulation and which provide rapid improvement of the female erectile response according to the present invention. However, the combinations of pharmaceutically active agent according to the present invention may be administered in other orally available dosage forms or by way of other drug delivery media as discussed in more detail above.

[0044] A preferred embodiment of the invention comprises about 5 mg to about 100 mg phentolamine mesylate in combination with about 5 mg to about 10 mg apomorphine.

[0045] Using the established oral dosages as starting points, the optimal dosage for the specific route of administration can be determined by measuring baseline arterial blood flow in genital circulation of the patient prior to administration of the drug using a doppler ultrasound velocimeter as described in Beehara, et al., *A Double-Blind Randomized Placebo controlled study comparing the Objective and Subjective Changes in Female Sexual Response Using Sublingual Apomorphine*. Journal of Sexual Medicine 1:209 (2004). Other methods such as thermography, plethysmography, radiometric or scintigraphic methods, and other methods well known in the art may also be utilized to assess blood flow in the genitalia. See Boolell et al., *Sildenafil, a novel effective oral therapy for male erectile dysfunction*. British

Journal of Urology, 78:257 (1996) and Boolell et al., *Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction.* International Journal of Impotence Research 8:47 (1996). Having established base line blood flow, various dosages of the respective vasodilators may be administered using the compositions encompassed by the present invention and their effect on blood flow may be measured. In addition, individual patients may be titrated with various dosages of the respective vasodilators until the optimum dosage is determined.

[0046] Preferred embodiments of the present invention for use in the treatment of female hypoactive sexual desire disorders involves administration of from about 5 mg to about 100 mg of phentolamine mesylate and about 5 to about 10 mg apomorphine in a rapidly dissolving oral formulation of the present invention from about 1 minute to about 1 hour prior to, and in preparation for intercourse. A preferential formulation involves administration of 40 mg of phentolamine mesylate and 6 mg apomorphine in a rapidly dissolving formulation to achieve peak serum apomorphine levels within an hour of administration (Figure 1), where peak levels represent 0.63 ng/ml and 2.11 ng/ml apomorphine. Shown in Figure 2.

[0047] The combination of 40 mg phentolamine and 6 mg of apomorphine appears to work together synergistically. The vasodilation action of the alpha-adrenergic antagonist phentolamine not only locally enhances the female erectile response at the genitalia, but also globally enhances dissemination of the dopaminergic agonist apomorphine, thereby minimizing first pass metabolism and breakdown of the active ingredient and to limit adverse side effects associated with the metabolic by-products. See Table 7.

[0048] This combination of alpha-adrenergic antagonist and dopaminergic agonist administered in a rapidly dissolving oral format combines the potency enhancing vassodilation properties of the former and the libido enhancing activity of the later in a way that minimizes the side effects of either administered singly or by other means. Together these properties provide an improved, on demand therapeutic treatment for female hypoactive desire disorder with minimal side effects.

Table 7:

Treatment-Related Adverse Events

	Phentolamine (40 mg)	Apomorphine (4 mg)	Phentolamine (40 mg) + Apomorphine (6 mg) (n=10)	Placebo
Rhinitis	7.7%	0%	1/10	3.8%
Headache	3.1%	5.2%	0/10	1.7%
Dizziness	2.0%	13.9%	0/10	0.2%
Tachycardia	1.5%	0%	0/10	0.6%
Vomiting	0%	2.6%	0/10	0%
Hypotension	0.2%	6.0%	0/10	0%
Nausea	0.7%	20.4%	1/10	0%

Example 2

Modulation of the Female Sexual Response.

[0049] As discussed above, the female erectile response takes place when under physical or psychological stimulation, blood flow to the genitalia increases by virtue of relaxation of smooth muscles in the arteries serving the genitalia. This physical response is enhanced by increased libido.

[0050] The compositions and methods of the present invention may be used to improve or enhance the sexual response in women whose sexual response is impaired as evidenced by diminished capacity to produce sufficient vaginal lubrication to facilitate comfortable penile penetration and by other symptoms of impaired sexual responsiveness that may be correlated with the erectile response.

[0051] In the absence of any other clinically diagnosed physical dysfunction in the female erectile response, the compositions and methods of the present invention may be used to enhance the normal female sexual response. The "on demand" aspect of the present invention will allow a more rapid response to sexual stimulation along with heightened sensation associated with excitement, plateau, and orgasmic stages of the female sexual response by virtue of the increased blood flow to the tissues.

[0052] The appropriate doses of the particular combinations of pharmaceutically active agents may be readily determined as described above. The female response may be measured using methods described in Masters, W. H. and Johnson, V. E., Human Sexual Response, Little, Brown, and Co., Boston (1966) which is incorporated herein by reference. Methods for measuring blood flow, including doppler ultrasonic velocimetry, thermography using for example an isothermal blood flow transducer, radioscintigraphic methods, and photoplethysmography may be used as well as other methods well known in the art. In addition, measuring the contraction of the distal third as is characteristic of the plateau phase of female sexual response of the vagina may be measured using methods and equipment well known in the art including but not limited to strain gauges or other devices for measuring muscular contraction or muscle tension.

[0053] Enhanced sexual response may also be measured in a more subjective manner by simply asking the female subject to describe any change in sensation brought about by administration of an alpha-adrenergic antagonist such as phentolamine mesylate and a dopaminergic agonist such as apomorphine the by the methods of the present invention. Appropriate placebo controls should also be conducted to ascertain whether or not the effort is directly attributable to the administration of the vasodilator.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating female hypoactive sexual desire disorder comprising administering to the gastrointestinal tract of a subject, a tablet or capsule comprising an alpha-adrenergic antagonist and a dopaminergic agonist and having a disintegration time of less than about twenty minutes, wherein the dopaminergic agonist is apomorphine

2. The method of claim 1, wherein the alpha-adrenergic antagonist is selected from the group consisting of phentolamine, phentolamine hydrochloride and phentolamine mesylate.

3. The method of claim 1, wherein the alpha-adrenergic antagonist is buspirone.

4. The method of claim 1, wherein the alpha-adrenergic antagonist is flibanserin.

5. The method of claim 1, wherein the dopaminergic agonist is apomorphine.

6. The method of claim 1, wherein the tablet or capsule comprises from about 5 mg to about 100 mg phentolamine.

7. The method of claim 2, wherein the tablet or capsule comprises about 40 mg phentolamine.

8. The method of claim 5, wherein the tablet or capsule comprises about 6 mg apomorphine.

9. The method of claim 1, wherein the tablet or capsule has a disintegration time of less than about ten minutes.

10. The method of claim 1, wherein the tablet or capsule has a disintegration time of less than about one minute.

11. The method of claim 1, wherein the tablet or capsule increases sexual responsiveness in from about 1 minute to about 60 minutes following administration.

12. The method of claim 1, wherein the tablet or capsule comprises apomorphine and phentolamine mesylate and has a disintegration time of less than about twenty minutes.

13. The method of claim 12, wherein the tablet or capsule has a disintegration time of less than about ten minutes.

14. The method of claim 12, wherein the tablet or capsule has a disintegration time of less than about one minute.

15. The method of claim 12, wherein the tablet or capsule is effective to improve sexual responsiveness in from about 1 minute to about 60 minutes following administration.

16. The method of claim 1, wherein the tablet or capsule comprises about 6 mg apomorphine and about 40 mg phentolamine mesylate and has a disintegration time of less than about twenty minutes.

17. The method of claim 16, wherein the tablet or capsule has a disintegration time of less than about ten minutes.

18. The method of claim 16, wherein the tablet or capsule has a disintegration time of less than about one minute.

19. The method of claim 16, wherein the tablet or capsule is effective to improve sexual responsiveness in from about 1 minute to about 60 minutes following administration.

Figure 1

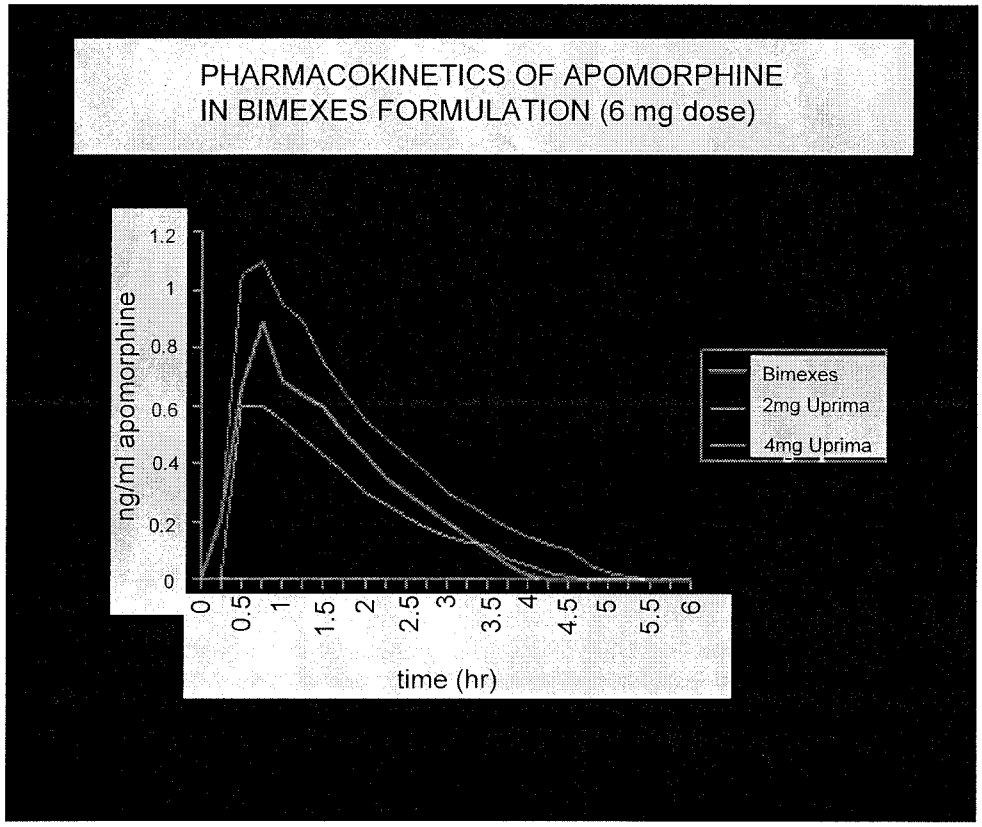
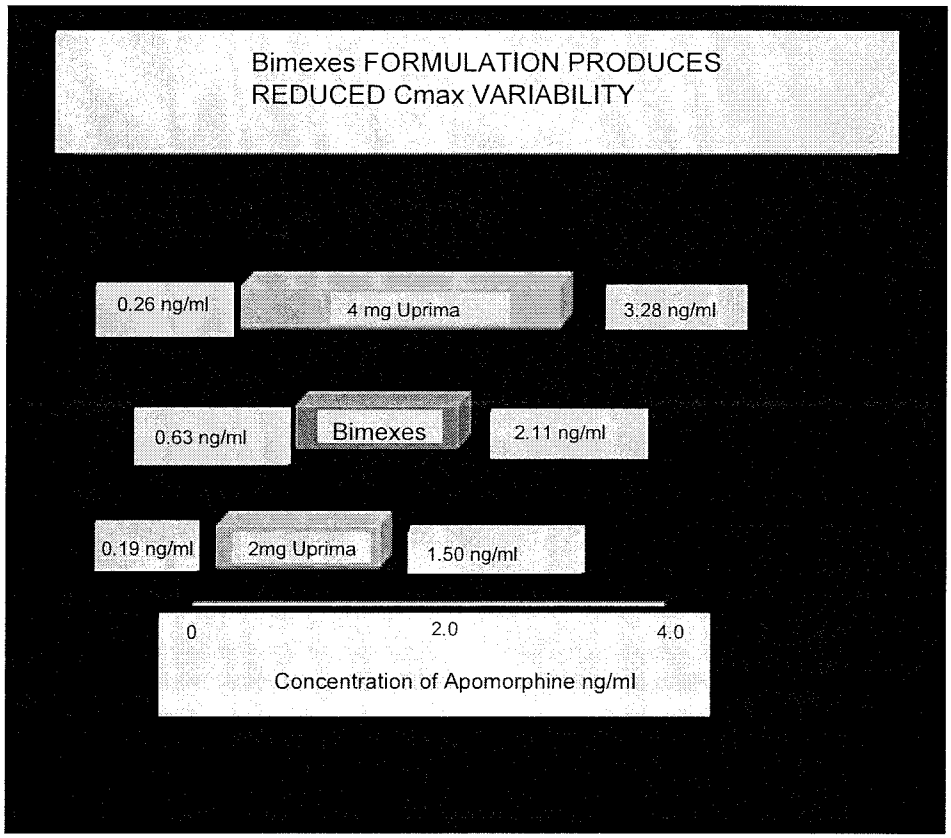

PHARMACOKINETICS OF APOMORPHINE
IN BIMEXES FORMULATION (6 mg dose)
ng/ml apomorphine
1.2
1
0.8
0.6
0.4
0.2
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
time (hr)
Bimexes
2mg Uprima
4mg Uprima

Figure 2


Bimexes FORMULATION PRODUCES
REDUCED Cmax VARIABILITY
0.26 ng/ml
4 mg Uprima
3.28 ng/ml
0.63 ng/ml
Bimexes
2.11 ng/ml
0.19 ng/ml
2mg Uprima
1.50 ng/ml
0
2.0
4.0
Concentration of Apomorphine ng/ml

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/65384

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/341, 31/472, 31/415 (2017.01)
CPC - A61K 31/21, 31/417, 31/472

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0071818 A1 (LARSEN, F) 29 March 2007; abstract; paragraphs [0002], [0022], [0030]-[0031], [0118]	1-19
Y	US 2004/0214824 A1 (MCCALL, RB et al.) 28 October 2004; abstract; paragraphs [0061]-[0062]	1-2, 6-7
Y	US 4,640,921 A (OTHMER, E et al.) 03 February 1987; abstract; column 2, lines 45-52	1, 3
Y	US 2007/0072872 A1 (BORSINI, F et al.) 29 March 2007; paragraphs [0002], [0012]	1, 4-5, 8-10
Y	US 5,731,339 A (LOWREY, F) 24 March 1998; abstract; column 3, lines 60-67	1, 11-19
Y	US 2007/0191320 A1 (YEAGER, JL et al.) 16 August 2007; abstract; paragraphs [0039], [0062]-[0063]	11, 15, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"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
17 January 2017 (17.01.2017)	17 FEB 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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