METHODS AND FORMULATIONS FOR MODULATING THE HUMAN SEXUAL RESPONSE

FIELD OF THE INVENTION

The application is directed to improved formulations for the administration of vasodilator agents to the blood circulation of a human in order to modulate the human sexual response on demand.

BACKGROUND OF THE INVENTION

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 an interplay between the autonomic nervous system, the endocrine system, and the circulatory system.

Failure of the erectile response is most common in men and is referred to as impotence. Impotence is the inability of a male to achieve or sustain a penile erection sufficient for vaginal penetration and intercourse. Numerous approaches have been taken in attempts to treat impotence. These approaches include the use of external or internally implanted penile prosthesis. (See, *e.g.*, U.S. Patent No. 5,065,744, to Zumanowsky). A variety of drugs and methods for administering drugs have also been used in attempts to treat impotence. For example, U.S. Patent No. 3,943,246 to Stürmer addresses treatment of impotence in men by buccal and peroral administration of daily doses of 300-1500 international units (I.U.) of oxytocin or daily divided doses of 150-250 I.U. of desamino-oxytocin. The patent states that the buccal administration of 100 I.U. three times a day for 14 days results in improvement of *impotentia erectionis* in 12 of the 16 patients treated.

U.S. Patent No. 4,530,920 to Nestor *et al.* suggests the possibility that administration of nonapeptide and decapeptide analogs of luteinizing hormone releasing hormone agonists may be useful in the induction or enhancement of sexual behavior or therapy for impotence or frigidity. Nestor *et al.* suggest numerous routes of administration of the analogs including buccal, sublingual, oral, parenteral (including subcutaneous, intramuscular, and intravenous administration), rectal, vaginal, and others.

U.S. Patent No. 4,139,617 to Grunwell *et al.* suggests buccal and other routes of administration of 19-oxygenated-androst-5-enes for the endocrine mediated enhancement of the libido in humans.

U.S. Patent No. 4,863,911 to Anderson *et al.* addresses methods for treating sexual dysfunction in mammals using a biooxidizable, blood-brain barrier penetrating estrogen derivative. One of the purported objects of the Anderson *et al.* invention is the treatment of "psychological impotence" in males. Test results showed that the drugs used in the study stimulated mounting behavior, intromission, and mount latency in castrated rats.

A number of publications have proposed the use of various vasodilators for the treatment of impotence in males. Attempts to utilize vasodilators for the treatment of impotence were prompted by the fact that a significant percentage of cases of impotence were noted to be vasculogenic, i.e. resulting from vascular insufficiency.

Voss *et al.*, U.S. Patent No. 4,801,587, issued January 31, 1989, addresses the use of an ointment containing a vasodilator and a carrier agent for topical application to the penis of impotent men. The Voss et al. patent also describes application of such an ointment into the urethra of the penis using a catheter as well as a multi-step regimen for applying a vasodilator to the skin of the penis. In addition, Voss et al. proposes the surgical removal of a portion of the fibrous sheath surrounding the corpora cavernosum, thereby facilitating the penetration of a vasodilator-containing

ointment into the corpora cavernosum. Vasodilators suggested for use by Voss et al. include papaverine, hydralazine, sodium nitroprusside, phenoxybenzamine, and phentolamine. The Voss et al. patent, however, provides no information regarding the actual efficacy of the treatments proposed or the nature of the response to such treatments.

U.S. Patent No. 4,127,118 to Latorre describes treating male impotence by direct injection of the vasodilating drugs into the corpus cavernosum and the corpus spongiosum of the penis using a syringe and one or more hypodermic needles. More particularly, the Latorre patent proposes the intracavernosal and intraspongiosal injection of sympathomimetic amines such as nylidrin hydrochloride, adrenergic blocking agents such as tolazoline hydrochloride, and direct acting vasodilators such as isoxsuprine hydrochloride and nicotinyl alcohol.

Brindley, G.S. (*Br. J. Pharmac.* 87:495-500, 1986) showed that, when injected directly into the corpus cavernosum using a hypodermic needle, certain smooth muscle relaxing drugs including phenoxybenzamine, phentolamine, thymoxamine, imipramine, verapamil, papaverine, and naftidrofuryl caused erection. This study noted that injection of an "appropriate dose of phenoxybenzamine or papaverine is followed by an unrelenting erection lasting for hours." Injection of the other drugs studied induced erections lasting from about 11 minutes to about 6.5 hours.

Zorgniotti *et al.*, *J. Urol.* 133:39-41 (1985) demonstrated that the intracavernosal injection of a combination of papaverine and phentolamine could result in an erection in otherwise impotent men. Similarly, Althof *et al.* *J. Sex Marital Ther.* 17(2): 101-112 (1991) reported that intracavernosal injection of papaverine hydrochloride and phentolamine mesylate resulted in improved erectile ability in about 84% of patients injected. However, in that study the dropout rate was 57%, fibrotic nodules developed in 26% of the patients, 30% of the patients developed abnormal liver function values, and bruising occurred in 19% of the patients.

Other studies describing intracavernosal injection of drugs using hypodermic needles for the treatment of impotence include: Brindley, *J. Physiol.* 342:24P (1983); Brindley, *Br. J. Psychiatr.* 143:312-337 (1983); Virag, *Lancet* ii:978 (1982); and Virag, *et al., Angiology* 35:79-87 (1984).

While intracavernosal injection may be useful for inducing erections in impotent men, the technique has numerous drawbacks. Obvious drawbacks include pain, risk of infection, inconvenience and interference with the spontaneity of the sex act. Priapism (prolonged and other painful erection) also appears to be a potential problem when using injection methods. See, *e.g.* Brindley, (1986). Another problem arising in some cases of intracavernosal injection involves the formation of fibrotic lesions in the penis. See, e.g., Corriere, *et al., J. Urol.* 140:615-617 (1988) and Larsen, *et al., J. Urol.* 137:292-293 (1987).

Phentolamine, which has been shown to have the potential to induce erection when injected intracavernosally, has also been the subject of oral administration to test its effects in men having non-specific erectile insufficiency (Gwinup, *Ann. Int. Med.* 15 July 1988, pp. 162-163). In that study, 16 patients ingested either a placebo or a 50 mg orally administered dose of phentolamine. Eleven of the 16 patients (including three placebo-treated patients) became tumescent, became more responsive to sexual stimulation, and were able to achieve an erection sufficient for vaginal penetration after waiting 1.5 hours to attempt intercourse.

Sonda *et al. J. Sex & Marital Ther.* **16(1):** 15-21 (year) reported that yohimbine ingestion resulted in subjective improvement in erectile ability in 38% of impotent men treated, but only 5% of the treated patients reported complete satisfaction.

Zorgniotti et al, PCT/US94/09048, describes the transmucosal administration of a variety of vasodilators including phentolamine mesylate for modulating the human sexual response.

Of interest to the background of the invention is the disclosure of Stanley *et al.*, U.S. Patent No. 4,885,173, which addresses methods administering drugs having cardiovascular or renal vascular activity through use of a lollipop assertedly facilitating drug absorption through the mucosal tissues of the mouth, pharynx, and esophagus. The Stanley *et al.* patent proposes that a large number of lollipop-administered drugs may improve cardiovascular function including drugs exhibiting direct vasodilating effects, including calcium channel blockers, β-adrenergic blocking agents, serotonin receptor blocking agents, angina blocking agents, other anti-hypertensive agents, cardiac stimulating agents, and agents which improve renal vascular function.

U.S. Patent No. 5,059,603 to Rubin describes the topical administration to the penis of isoxsuprine and caffeine, and nitroglycerine and caffeine along with suitable carrier compounds for the treatment of impotence.

There continues to exist a need in the art for effective means for modulating human sexual response and especially for enhancing erectile ability in males suffering from impotence. Ideally, such means would be convenient and simple to use, would not require a constant dosage regimen or even multiple doses to achieve desired results, would be non-invasive and would allow a rapid and predictable capacity for onset of erectile function on demand and in response to normal sexual stimulation.

All of the references set out in this specification are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention provides improved formulations for modulating the human sexual response in a human by administering a vasodilator agent to the circulation in an amount effective to increase blood flow to the genitalia. According to the invention, modulation of male and female human sexual response is provided on demand by administering an

effective vasodilating amount of the agent in an oral formulation. Vasodilating agents useful in the present invention include, but are not limited to, the group consisting of phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine, yohimbine, organic nitrates (e.g. nitroglycerin), thymoxamine, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline and papaverine. The presently preferred vasodilator agent is phentolamine mesylate. The presently preferred oral formulation comprises in combination, a vasodilator agent in a rapidly dissolving tablet. Preferred rapidly dissolving tablets have a disintegration time of 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 from about 5 mg to about 80 mg.

The present invention is also directed to a vasodilator formulation comprising in combination, a vasodilator and a chewable tablet.

The present invention is specifically directed to improved methods for treating male impotence, by administering a vasodilator agent in an amount effective to increase blood flow to the penis wherein erectile ability on demand is permitted by oral administration of the vasodilator.

Preferably, the amount of vasodilating agent used in the practice of the invention for treatment of male impotence is effective to improve erectile ability in from about 1 minute to about 60 minutes following administration of the agent.

The invention is also specifically directed to methods for modulating the excitation and plateau phases of the female sexual response on demand by oral administration of an effective amount of vasodilator agent.

The methods of the present invention are also useful in preparation for sexual intercourse by virtue of the ability to modulate the sexual response in both males and females.

The present invention is also directed to the use of a drug having vasodilator activity for the manufacture of a medicament for oral administration to modify, on demand, the sexual response in a human and more particularly to improve erectile ability in response to sexual stimulation. Vasodilator drugs useful for manufacturing the medicament include, but are not limited to, phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine yohimbine, organic nitrates, thymoxamine, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine.

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.

DETAILED DESCRIPTION

The human sexual response in both the male and female involves a complex interplay between endocrine, neurological and psychological components which result in certain physiological and anatomical responses in both men and women.

While there are obvious differences in the sexual response between men and women, one common aspect of the sexual response is the erectile response. The erectile response in both males and females is result of engorgement of the erectile tissues of the genitalia with blood in response to sexual stimulation (physical, psychological, or both).

The vasculature which serves erectile tissue in both men and women is similar. In particular, in both men and women, the arterial circulation to the erectile tissues of the genitalia derives from the common iliac artery which branches from abdominal aorta. The common iliac artery bifurcates into the internal and external iliac arteries. The internal pudic artery arises from the smaller of two terminal branches of the anterior trunk of the internal iliac artery. In the female, the internal pudic artery branches into the superficial perineal artery which supplies the labia pudenda. The

internal pudic artery also branches into the artery of the bulb which supplies the bulbi vestibuli and the erectile tissue of the vagina. The artery of the corpus cavernosum, another branch of the internal pudic artery supplies the cavernous body of the clitoris. Still another branch of the internal pudic artery is the arteria dorsalis clitoridis which supplies the dorsum of the clitoris and terminates in the glans and membranous folds surrounding the clitoris which correspond to the prepuce of the male.

In the male, the internal pudic artery branches into the dorsal artery of the penis (which itself branches into a left and right branch) and the artery of the corpus cavernosum, all of which supply blood to the corpus cavernosum. The dorsal artery of the penis is analogous to the artery dorsalis clitoridis in the female, while the artery of the corpus cavernosum in the male is analogous to the artery of the same name in the female.

The male erectile response is regulated by the autonomic nervous system which controls blood flow to the penis via the interaction of peripheral nerves associated with the arterial vessels in and around the corpus cavernosum. In the non-aroused or non-erect state, the arteries serving the corpus cavernosum are maintained in a relatively constricted state, thereby limiting the blood flow to the corpus cavernosum. However, in the aroused state, the smooth muscles associated with the arteries relax under the influence of catecholamines and blood flow to the corpus cavernosum greatly increases, causing expansion and rigidity of the penis. Brindley, *supra* (1986) hypothesizes that smooth muscle contraction opens valves through which blood can flow from the corpus cavernosum into the extracavernosal veins. According to Brindley (1986), when the relevant smooth muscles relax, the valves close diminishing venous outflow from the corpus cavernosum. When accompanied by increased arterial blood flow into the corpus cavernosum, this results in engorgement of the corpus cavernosum and an erection.

The pre-orgasmic sexual response in females can be broken down into distinct phases. Both the excitement phase and the plateau phase

involve vasodilation and engorgement (vasocongestion) of the genitalia with arterial blood in a manner analogous to the male erectile response.

The excitement phase of the female sexual response is characterized by vasocongestion in the walls of the vagina which leads to the transudation of vaginal fluids and vaginal lubrication. Further, the inner one-third of the vaginal barrel expands and the cervix and the body of the uterus become elevated. This is accompanied by the flattening and elevation of the labia majora and an increase in clitoral size. [Kolodny *et al.*, *Textbook of Sexual Medicine*, Little and Brown, Boston, MA (1979)].

The plateau phase follows the excitement phase in the female sexual response and is characterized by prominent vasocongestion in the outer one-third of the vagina, causing a narrowing of the opening of the vagina and a retraction of the shaft and the glans of the clitoris against the symphysis pubis. These responses are also accompanied by a marked vasocongestion of the labia. [Kolodny, *supra* (1979)].

The vasocongestive aspects of the female sexual response are not restricted to the genitalia in that areolar engorgement also occurs, sometimes to the extent that it masks the antecedent nipple erection that usually accompanies the excitement phase.

The failure of the erectile response in men to the extent that vaginal penetration and sexual intercourse cannot be achieved is termed impotence. Impotence has numerous possible causes which can be broken down into several general classifications. Endocrine related impotence can result from primary gonadal failure, advanced diabetes mellitus, hypothyroidism, and as one of the secondary sequelae of pituitary adenoma, idiopathic or acquired hypogonadism, hyperprolactinemia and other endocrine abnormalities.

Chronic systemic illnesses such as cirrhosis, chronic renal failure, malignancies and other systemic diseases can also cause impotence. Neurogenic impotence arising in the central nervous system can be caused by

temporal lobe disorders caused by trauma, epilepsy, neoplasms and stroke, intramedullary spinal lesions, paraplegia, and demyelinating disorders. Neurogenic causes of impotence arising in the peripheral nervous system include somatic or autonomic neuropathies, pelvic neoplasms, granulomas, trauma, and others. Urologic causes of impotence include complete prostatectomy, local trauma, neoplasms, Peyronie's disease, and others. In addition, as discussed above, a significant percentage of cases of impotence are vasculogenic in nature.

As many as half the cases of male impotence may be psychogenic because there is no readily-ascertainable organic cause for the disorder. Even when there appears to be an underlying organic cause of impotence, psychologic factors may play a role in the disorder.

The present invention is designed to modify the circulatory aspects of the erectile response on demand using vasoactive agents administered to the circulation using a rapidly dissolving orally administered formulation.

A number of vasoactive agents may be used in the practice of the present invention based on demonstrated systemic efficacy as vasodilators. Useful vasodilating drugs include those generally classified as α-adrenergic antagonists, sympathomimetic amines and those agents which exhibit direct relaxation of vascular smooth muscle. Exemplary α-adrenergic antagonists include phentolamine hydrochloride, phentolamine mesylate, phenoxybenzamine, tolazoline, dibenamine, yohimbine, and others. Phentolamine mesylate is a preferred α-adrenergic agent vasodilator for use preferred practice of the present invention. An exemplary sympathomimetic amine contemplated for use in the method of the present invention is nylidrin and use of other sympathomimetic amines having vasodilating activity is also contemplated.

Nicotinic acid (or nicotinyl alcohol) has a direct vasodilating activity useful in the practice of the present invention. Also contemplated is

the use of papaverine, a non-specific smooth muscle relaxant which possesses vasodilating activity and which has been used to treat male impotence by direct injection into the corpus cavernosum either alone or in combination with other drugs such as phentolamine. Organic nitrates such as nitroglycerine and amyl nitrate have pronounced vasodilating activity by virtue of their ability to relax vascular smooth muscle and are thus contemplated for use according to the invention. Other vasoactive drugs useful in the practice of the present invention include, without limitation, thymoxamine, imipramine, verapamil, naftidrofuryl, and isoxsuprine.

The formulations also eliminate the need for continuous therapy by providing a single dose for rapidly improving erectile ability on demand.

According to the present invention, the vasodilating agent is administered orally in the form of a rapidly dissolving tablet formulation, a rapidly dissolving chewable tablet formulation, solutions, effervescent formulations, and other orally administered formulations that permit the rapid introduction of the vasodilating substance to the circulation so as to improve erectile ability within a short time (on demand) after administration of a single dose of the agent.

Formulations and methods of the present invention are thus more convenient and help minimize any side-effects that may arise as a result of continuous or daily administration of the drugs. In addition, methods of the present invention allow more spontaneity in sexual activity than allowed by other methods such as the intracavernosal injection of vasodilators.

The examples set forth below are intended to be illustrative of the present invention and are not intended to limit the scope of the invention as set out in the appended claims.

Example 1 describes rapidly dissolving formulations for the oral administration of vasodilating agents. Example 2 describes the bioavailability of phentolamine mesylate when administered using a rapidly dissolving oral formulation. Example 3 describes the effect of the administration of a rapidly

dissolving oral formulation of phentolamine mesylate on male erectile ability. Example 4 describes other vasoactive agents useful in modulating the human sexual response. Example 5 addresses the practice of the present invention in modulating the erectile response in females.

EXAMPLE 1

RAPIDLY DISSOLVING FORMULATIONS FOR THE ORAL ADMINISTRATION OF VASODILATING AGENTS

The present invention is directed to rapidly dissolving orally administered formulations for the rapid delivery of vasodilating agents to the systemic circulation thereby allowing a rapid (on demand) onset of improved erectile ability in response to sexual stimulation. The invention is also directed to other orally administered formulations for "on demand" improvement in erectile ability in response to sexual stimulation including chewable tablets, effervescent formulations, solutions, lozenges, troches, powders, solutions, suspensions, emulsions, or encapsulated powders which can be of the gelatin type or other types.

An exemplary formulation of a rapidly dissolving tablet that includes phentolamine mesylate is set out in Table 1.

TABLE 1

	mg/tablet
Phentolamine Mesylate, USP	40
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	212
Microcrystalline Cellulose, NF	120
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

The ingredients set out in Table 1 (and those used tablet formulations set out below) were 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.

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.

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* which is also incorporated herein by reference. Preferred disintegration times for the practice of the present invention are less then 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 parmaco kinetic properties of the vasodilator agent itself.

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.

Another example of a rapidly disintegrating tablet formulation is described in U.S. patent no. 5,298,261 to Pebley et al., (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, xanthin, carrageenan, or tragacanth. Preferred carbohydrates described in the '261 patent include mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, or corn syrup solids.

Another rapidly dissolving formulation is described in U.S. patent no. 5,079,018 to Ecanow (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.

The above formulations are given by way of example and other rapidly dissolving formulations will be apparent to those of skill in the art.

EXAMPLE 2

BIOAVAILABILITY OF PHENTOLAMINE MESYLATE AS A RAPIDLY DISSOLVING, ORALLY ADMINISTERED FORMULATION

Preliminary studies were conducted to compare the bioavailability of a single 40 mg dose of phentolamine mesylate when administered in the form of an orally administered rapidly dissolving tablet, with the bioavailability of phentolamine mesylate when orally administered in a standard release hard tablet.

Rapidly dissolving tablets containing 40 mg of phentolamine mesylate were prepared as described in Table 1. Standard release hard tablets containing 40 mg of phentolamine mesylate were prepared as follows:

Table 2

Standard Release Hard Tablet

	mg/tablet
Phentolamine Mesylate, USP	40
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Dicalcium Phosphate Dibasic, USP	228
Microcrystalline Cellulose, NF	120
Total Tablet Weight	400

Tablets were formed by direct compression. Physical characteristics of tablets prepared according to Table 2 include a hardness of 11.5 Kp, average tablet thickness of 0.16 inches, and an average disintegration time of about 26.33 minutes.

In preliminary studies, a single dose of 40 mg of phentolamine either in the rapidly dissolving tablet formulation or in the standard release hard tablet were administered to a group of volunteers.

Five (5) ml blood samples were collected from each individual at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.5 and 2 hours after administration of the formulation and the plasma level of phentolamine was determined using gas chromatography with electron capture detection as follows.

Phentolamine (CIBA GEIGY AG) and an internal standard, BA11038 (CIBA GEIGY AG) were extracted from alkalinized human heparinized plasma with 5% isopropyl alcohol in toluene. The compounds of interest were back extracted from the organic layer with an acid solution (e.g., 0.05 M sulfonic acid), alkalinized again, and extracted with 5% isopropyl alcohol in toluene. Organic solvent was then evaporated and the dried extracts were reconstituted with hexane and derivatized with heptafluorobutyryl-imidazole. The extracts were then washed and reconstituted with hexane. Extracts were then analyzed by injection into a gas chromatograph equipped with a DB-5 wide bore capillary column and an electron capture detector. The linear range of phentolamine concentration by this method was 5-400 ng/ml and the lower limit of accurate quantitation was 5 ng/ml. Levels of phentolamine were determined by comparison to a standard curve generated using known concentrations of phentolamine in solution processed using the procedure described above.

Table 3 sets out the plasma phentolamine concentration in volunteers receiving a 40 mg dose of phentolamine mesylate in a standard release hard tablet formulation shown in Table 2 at various times after administration.

Table 3

Individual and Mean Plasma Phentolamine Concentrations (ng/ml) After Administration of 40 mg Phentolamine Mesylate in a Standard Release Hard Tablet

VOLN	0.25 hr	0.50 hr	0.75 hr	1.00 hr	1.50 hr	2.00 hr
1	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0
2	<5.0	<5.0	<5.0	<5.0	<5.0	8.3
3	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0
MEAN	0.0	0.0	0.0	0.0	0.0	2.8
STD.DEV.	0.0	0.0	0.0	0.0	0.0	4.8
C.V. (%)	0	0	0	0	0	171
S.E.M.	0.0	0.0	0.0	0.0	0.0	2.8
N	3	3	3	3	3	3
MIN	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0
MAX	<5.0	<5.0	<5.0	<5.0	<5.0	8.3

As can be seen in Table 3, quantifiable levels of phentolamine were detected in only one of the three volunteers tested and were detected only at 2 hours after administration of the tablet.

However, as can be seen in Table 4 below, when the same volunteers were given a 40 mg dose of phentolamine mesylate in the rapidly dissolving tablet formulation shown in Table 1, quantifiable levels of phentolamine were detected in plasma as early as 0.25 hours after administration with a peak plasma level occurring between 0.5 hours and 0.75

hours after administration while falling below quantifiable levels between 1.5 hours and 2.0 hours after administration.

Table 4

Individual and Mean Plasma Phentolamine Concentrations (ng/ml) After Administration of 40 mg Phentolamine Mesylate in Rapidly Dissolving Tablet

Volunteer	0.25 hr	0.50 hr	0.75 hr	1.00 hr	1.50 hr	2.00 hr
1	14.0	22.6	17.9	13.7	6.2	<5.0
2	11.2	15.9	14.7	12.6	6.6	<5.0
3	13.7	13.2	10.3	9.9	7.2	<5.0
MEAN	13.0	17.2	14.3	12.1	6.7	0.0
STD.DEV.	1.5	4.8	3.8	2.0	0.5	0.0
C.V. (%)	11.5	27.9	26.6	16.5	7.5	0
S.E.M.	0.9	2.8	2.2	1.2	0.3	0.0
N	3	3	3	3	3	3
MIN	11.2	13.2	10.3	9.9	6.2	<5.0
MAX	14.0	22.6	17.9	13.7	7.2	<5.0

In view of the data shown above that demonstrating that the rapidly dissolving oral formulation of phentolamine mesylate allows more rapid absorption of phentolamine mesylate into the blood stream than the standard release oral formulations, a more extensive study of bioavailability of several dosage levels of phentolamine mesylate administered in the rapidly dissolving oral formulation described above (40 mg phentolamine mesylate) were conducted. The formulations were prepared as follows:

Table 5

	mg/tablet
Phentolamine Mesylate, USP	20
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	232
Microcrystalline Cellulose, NF	120
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

Table 6

	mg/tablet
Phentolamine Mesylate, USP	60
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	192
Microcrystalline Cellulose, NF	120
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

After mixing of the ingredients, tablets were prepared by direct compression. Physical characteristics of the tablets prepared according to Tables 5 and 6 were very similar to those described for tablets prepared according to Table 1.

In this study, seven male subjects were selected based on medical history and physical examination. All patients had an impotence of organic etiology with a duration of less than 3-4 years.

In this study, subject males were given one of the above-indicated formulations of phentolamine mesylate in the indicated doses. Five

milliliters of blood were collected from each patient at pre-dose and 0.083, 0.125, 0.167, 0.250, 0.50, 0.750, 1.0, 1.5, 2.0, 4.0, 6.0, and 8 hours following the dose and the plasma level of phentolamine was measured as described above.

Tables 7, 8, and 9 show the results of these studies.

Table 7 illustrates the plasma level of phentolamine mesylate after administration of a 20 mg dose of drug in the rapidly dissolving oral tablet formulation as shown in Table 5.

Table 7

Individual and Mean Plasma Phentolamine Concentrations (ng/mL) for Phentolamine Mesylate 20 mg Rapidly Dissolving Tablet

VOLN	0.000 hr	0.083 hr	0.125 hr	0.167 hr	0.250 hr	0.500 hr	0.750 hr	1.000 hr	1.500 hr	2.000 hr	4.000 hr	6.000 hr	8.000 hr
1	<5.0	<5.0	<5.0	<5.0	<5.0	6.7	9.6	11.4	7.8	6.2	<5.0	<5.0	<5.0
2	<5.0	<5.0	<5.0	<5.0	<5.0	8.1	6.0	<5.0	5.9	<5.0	<5.0	<5.0	<5.0
3	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	9.0	9.1	<5.0	<5.0	<5.0	<5.0	<5.0
4	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	7.7	<5.0	<5.0	<5.0	<5.0
5	<5.0	<5.0	<5.0	<5.0	8.2	6.6	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0
6	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	7.1	<5.0	<5.0	<5.0	<5.0
7	<5.0	<5.0	<5.0	<5.0	10.3	16.7	10.9	7.2	<5.0	<5.0	<5.0	<5.0	<5.0
MEAN	0.0	0.0	0.0	0.0	2.6	5.4	5.1	4.0	4.1	0.9	0.0	0.0	0.0
STD.DEV.	0.0	0.0	0.0	0.0	4.6	6.1	5.0	5.1	3.9	2.3	0.0	0.0	0.0
C.V. (%)	0	0	0	0	177	113	98.0	128	95.1	256	0	0	0
S.E.M.	0.0	0.0	0.0	0.0	1.7	2.3	1.9	1.9	1.5	0.9	0.0	0.0	0.0
N	7	7	7	7	7	7	7	7	7	7	7	7	7
MIN	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0
MAX	<5.0	<5.0	<5.0	<5.0	10.3	16.7	10.9	11.4	7.8	6.2	<5.0	<5.0	<5.0

As seen in Table 7, mean plasma phentolamine levels peak at about 5.4 ng/ml with the peak occurring between 0.25 hours and 0.50 hours, with a subsequent fall off in phentolamine level beginning between 0.50 hours and 0.75 hours.

Table 8 illustrates mean plasma levels of phentolamine after administration of a 40 mg dose in the rapidly dissolving oral formulation shown in Table 1.

Table 8

Individual and Mean Plasma Phentolamine Concentrations (ng/mL) for Phentolamine Mesylate 40 mg Tablet

VOLN	0.000 hr	0.083 hr	0.125 hr	0.167 hr	0.250 hr	0.500 hr	0.750 hr	1.000 hr	1.500 hr	2.000 hr	4.000 hr	6.000 hr	8.000 hr
1	<5.0	<5.0	<5.0	<5.0	8.2	38.2	25.9	16.3	11.6	8.7	6.3	<5.0	<5.0
2	<5.0	<5.0	<5.0	6.1	13.0	20.1	13.5	10.5	10.0	7.7	<5.0	<5.0	<5.0
3	<5.0	<5.0	<5.0	<5.0	8.0	20.6	15.9	14.3	13.7	9.6	<5.0	<5.0	<5.0
4	<5.0	<5.0	5.6	5.4	8.2	11.8	17.9	15.3	10.6	9.2	5.3	<5.0	<5.0
5	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	9.7	9.3	<5.0	<5.0	<5.0
6	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	11.0	15.1	17.0	11.4	<5.0	<5.0	<5.0
7	<5.0	<5.0	<5.0	<5.0	6.8	26.2	NS	20.0	14.4	10.8	<5.0	<5.0	<5.0
MEAN	0.0	0.0	0.8	1.6	6.3	16.7	14.0	13.1	12.4	9.5	1.7	0.0	0.0
STD.DEV.	0.0	0.0	2.1	2.8	4.7	13.9	8.6	6.4	2.7	1.2	2.8	0.0	0.0
C.V. (%)	0	0	263	175	74.6	83.2	61.4	48.9	21.8	12.6	165	0	0
S.E.M.	0.0	0.0	0.8	1.1	1.8	5.3	3.5	2.4	1.0	0.5	1.1	0.0	0.0
N	7	7	7	7	7	7	6	7	7	7	7	7	7
MIN	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	9.7	7.7	<5.0	<5.0	<5.0
MAX	<5.0	<5.0	5.6	6.1	13.0	38.2	25.9	20.0	17.0	11.4	6.3	<5.0	<5.0

These data show that the mean plasma levels of phentolamine peak at about 16.7 ng/ml with the peak occurring at around 0.5 hours after administration while quantifiable levels of drug were maintained for as long as 2 hours after administration with two patients showing quantifiable levels for as long as 4 hours after administration.

Table 9 illustrates individual and mean plasma phentolamine concentrations in plasma after administration of a 60 mg dose of phentolamine mesylate in the rapidly dissolving oral formulation shown in Table 6.

Table 9
Individual and Mean Plasma Phentolamine Concentrations (ng/mL)
for Phentolamine Mesylate 60 mg Tablet

VOLN	0.000 hr	0.083 hr	0.125 hr	0.167 hr	0.250 hr	0.500 hr	0.750 hr	1.000 hr	1.500 hr	2.000 hr	4.000 hr	6.000 hr	8.000 hr
1	<5.0	<5.0	<5.0	<5.0	8.1	20.1	15.5	13.4	16.3	18.6	12.4	5.3	<5.0
2	<5.0	<5.0	<5.0	<5.0	<5.0	42.2	41.0	25.1	17.2	13.7	8.1	<5.0	<5.0
3	<5.0	<5.0	<5.0	<5.0	<5.0	15.4	38.2	43.8	27.7	16.3	7.1	<5.0	<5.0
4	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	13.7	32.1	23.5	14.6	8.0	<5.0	<5.0
5	<5.0	<5.0	<5.0	<5.0	<5.0	20.1	18.4	12.2	10.3	6.7	<5.0	<5.0	<5.0
6	<5.0	<5.0	<5.0	5.7	11.8	12.8	21.2	17.4	25.2	13.5	5.8	<5.0	<5.0
7	<5.0	<5.0	<5.0	5.3	24.6	49.7	46.1	37.7	25.3	16.7	8.3	<5.0	<5.0
MEAN	0.0	0.0	0.0	1.6	6.4	22.9	27.7	26.0	20.8	14.3	7.1	0.8	0.0
STD.DEV.	0.0	0.0	0.0	2.7	9.4	17.3	13.5	12.3	6.3	3.8	3.7	2.0	0.0
C.V. (%)	0	0	0	169	147	75.5	48.7	47.3	30.3	26.6	52.1	250	0
S.E.M.	0.0	0.0	0.0	1.0	3.6	6.5	5.1	4.6	2.4	1.4	1.4	0.8	0.0
N	7	7	7	7	7	7	7	7	7	7	7	7	7
MIN	<5.0	<5.0	<5.0	<5.0	<5.0	<5.0	13.7	12.2	10.3	6.7	<5.0	<5.0	<5.0
MAX	<5.0	<5.0	<5.0	5.7	24.6	49.7	46.1	43.8	27.7	18.6	12.4	5.3	<5.0

The results in Table 9 show that near the plasma levels in patients receiving 60 mg of phentolamine in a rapidly dissolving oral formulation peaked at about 2.27 ng/ml with the peak occurring at around 0.75 hours after administration while quantifiable levels of drug remained in the plasma for at least 4 hours after administration.

While the studies described above were conducted using a rapidly dissolving formulation, other formulations that allow rapid absorption of an active vasodilator agent and corresponding improvement in erectile ability are within the scope of the present invention. For example, the present invention also includes a chewable tablet formulation shown in Table 10.

Table 10

	mg/tablet
Phentolamine Mesylate, USP	40
Silicon Dioxide, NF	12
Stearic Acid, NF	12
Lactose, NF	100
Sweetrex	348
Aspartame	40
ProSweet	8
Peppermint Flavor #860-172	40
Total Tablet Weight	600

EXAMPLE 3

EFFECT OF THE ADMINISTRATION OF RAPIDLY DISSOLVING ORAL FORMULATION OF PHENTOLAMINE MESYLATE ON MALE ERECTILE ABILITY

In order to test the ability of a rapidly dissolving oral formulation of phentolamine mesylate on erectile ability, a single blind trial was conducted.

All patients had impotence of organic etiology. Patients were selected for inclusion in the trial based medical history and physical examination with a duration of impotence of less than 3-4 years. Each patient was given two tablets: a rapidly dissolving tablet containing 40 mg of phentolamine mesylate (see Table 1), and a placebo tablet lacking phentolamine mesylate.

Patients were asked to take one tablet 20 to 30 minutes before attempting coitus. One or more days after using the first tablet, the patients repeated the process with the second tablet.

Patients were advised not to consume alcohol prior to using the tablets and were told not to expect erection without sexual stimulation. Patients were told that either tablet might prove beneficial and were told to report results in terms of erection and vaginal penetration or failure to achieve an erection sufficient for vaginal penetration. Patients were also asked to report side effects. Results of this study are illustrated in Table 10.

Table 11

Group	Tablet A (drug) S	U	Tablet B (placebo) S	U
A	2	2	0	4
B	1	3	0	4
Total	3	5	0	8

S = Erection sufficient for vaginal penetration

U = Erection Insufficient for vaginal penetration

As can be seen in Table 11, 50% of patients in Group A who took the rapidly dissolving oral formulation were able to achieve erection sufficient for vaginal penetration within 30 minutes of administration of the drug while 33% of the patients in Group B had success. Also, as shown in Table 10, there were no placebo responders.

Although significant success was achieved using a 40 mg dose of phentolamine mesylate, it is expected that doses ranging from about 5 mg to about 100 mg of phentolamine will be useful in the practice of the present invention.

EXAMPLE 4

VASOACTIVE AGENTS USEFUL IN MODULATING THE HUMAN SEXUAL RESPONSE

A number of other vasoactive agents may be used in the practice of the present invention based on their demonstrated efficacy as vasodilators. Useful vasodilating drugs include those generally classified as α-adrenergic antagonists, sympathomimetic amines and those agents which exhibit direct relaxation of vascular smooth muscle.

Exemplary α-adrenergic antagonists include phentolamine hydrochloride, phentolamine mesylate, phenoxybenzamine, tolazoline, dibenamine, yohimbine, and others. Phentolamine mesylate is preferred in the practice of the present invention. An exemplary sympathomimetic amine contemplated for use in the method of the present invention is nylidrin although other sympathomimetic amines having vasodilating activity are also comprehended by the invention.

Nicotinic acid (or nicotinyl alcohol) has a direct vasodilating activity which is useful in the practice of the present invention. Papaverine is also non-specific smooth muscle relaxant which has vasodilating activity and has been used to treat male impotence by direct injection into the corpus cavernosum either alone or in combination with other drugs such as phentolamine.

Organic nitrates such as nitroglycerine and amyl nitrate also have pronounced vasodilating activity by virtue of their ability to relax vascular smooth muscle. Other vasoactive drugs of use in the practice of the present invention include but are not limited to thymoxamine, imipramine, verapamil, naftidrofuryl, isoxsuprine, and others.

In the practice of the present invention, these vasoactive 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 vasodilating agent to the systemic circulation and which provide the on demand of advantages of the present invention.

Appropriate doses of each vasoactive agents for each route of administration are readily determined by those of ordinary skill in the art. By way of illustration, in order to determine the appropriate dose of each of the vasodilating agents of the present invention, one of ordinary skill in the art may use as a starting point, the usual published dosage of the vasodilator. The usual oral doses for commercially available vasodilators can be found in

the Physician's Desk Reference published annually by Medical Economic Data, Montvale New Jersey, and in the available medical literature.

By way of example, Pavabid® oral papaverine hydrochloride is available from Marion Merrell Dow and is normally administered at 150 mg every 12 hours to achieve its vasodilating effects.

The oral dose of Calon® (verapamil hydrochloride) available from Searle is determined by titrating the individual patient with from 120 mg to about 240 mg of drug every 12 hours, the specific dose depending on the individual patient's response to the drug.

Yohimbine hydrochloride available as Daytohimbin® (Dayton Pharmaceuticals), Yocon® (Palisades Pharmaceuticals), and Yohimex® (Kramer) are all administered orally as 5.4 mg three times a day.

Imipramine hydrochloride is available as Tofranil® from Geigy and is administered orally 4 times a day for a total dose ranging from 50 mg to about 150 mg per day.

Imipramine pamoate, also available from Geigy is administered in oral maintenance doses of 150 mg/day.

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 Zorgniotti *et al.*, PCT/US94/09048. 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. Having established base line blood flow, various dosages of the respective vasodilators may be administered using the formulations encompassed by the present invention and their effect on blood flow may be measured. The magnitude of the increase in blood flow necessary to modulate or enhance the sexual response in humans may vary from individual to individual, but is readily determined as described in Zorgniotti *et al.*

PCT/US94/09048. In addition, individual patients may be titrated with various dosages of the respective vasodilators until the optimum dosage is determined.

Vascular flow studies may also be coupled with assessments of sexual responsiveness as evidenced by the improvement of erectile ability in response to sexual stimulation.

EXAMPLE 5

MODULATION OF THE FEMALE SEXUAL RESPONSE

As discussed above, there are striking parallels between the vascular anatomy of male and female genitalia and in the erectile response facilitated by this vasculature. In both males and females, the 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.

The methods and formulations of the present invention may be used to improve or enhance the erectile 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.

As in the case of male sexual response, in the absence of any clinically diagnosed dysfunction in the female erectile response, the 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 and plateau stages of the female sexual response by virtue of the increased blood flow to the tissues.

In practice, enhancement of the female sexual response using the methods of the present invention are carried in much the same way as those described for males as described above.

An effective vasodilating dose of a vasodilating agent is administered to a woman the formulations of the present invention. The appropriate doses of the particular vasodilating agent may be readily determined using methods described in Example 4. 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, photoplethysmography may be used as well as other methods well known in the art. In addition, measuring the contraction of the distal 1/3 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.

In addition, enhanced sexual response may be measured in a more subjective manner by simply asking the female subject to describe any change in sensation brought about by administration of the vasodilator 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.

Preferred embodiments of the present invention involves the administration of from about 5 mg to about 80 mg of phentolamine mesylate 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. However any of the vasodilating agents included within the scope of the present invention may be used.

While this invention has been described by way of preferred embodiments, the examples set out herein are not intended to limit the scope of the invention which contemplates the use of any pharmacologic vasodilating drug capable of absorption into the systemic circulation upon administration of the drug via an orally administered formulation capable of improving erectile ability on demand.

THIS SHEET HAS BEEN REPLACED

What is claimed is:

1. The use of a vasodilator for the manufacture of a rapid acting formulation for modulating human sexual response, the formulation being capable of delivering to the blood circulation of a human an amount of the vasodilator effective to modulate the sexual response on demand.

2. The use of claim 1 wherein the vasodilator is selected from the group consisting of phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine, yohimbine, nitroglycerine, thymoxamine, nicotinyl alcohol, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine.

3. The use of claims 1 or 2 wherein the formulation comprises a rapidly dissolving orally administrable vasodilator formulation.

4. The use of claims 1, 2 or 3 wherein the vasodilator is phentolamine mesylate.

5. The use of a vasodilator for the manufacture of an orally administrable rapid acting formulation for the treatment of impotence, the formulation being capable of delivering to the blood circulation of an impotent male an amount of the vasodilator effective to improve the sexual responsiveness on demand.

6. The use of claim 5 wherein the vasodilator is selected from the group consisting of phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine, yohimbine, nitroglycerine, thymoxamine, nicotinyl alcohol, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine.

7. The use of claims 5 or 6 wherein the formulation is a rapidly dissolving orally administrable vasodilator formulation.

8. The use of claims 5, 6 or 7 wherein the vasodilator is phentolamine mesylate.

This Sheet Has Been Replaced