



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : A61K 31/00</p>	<p>A2</p>	<p>(11) International Publication Number: WO 00/59491 (43) International Publication Date: 12 October 2000 (12.10.00)</p>
<p>(21) International Application Number: PCT/US00/09112 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 60/127,910 6 April 1999 (06.04.99) US (71) Applicant (for all designated States except US): ZONAGEN, INC. [US/US]; 2408 Timberloch Place, B-4, The Woodlands, TX 77380 (US). (72) Inventor: ZORGNIOTTI, Andrian (deceased). (72) Inventor; and (75) Inventor/Applicant (for US only): PODOLSKI, Joseph, S. [-/US]; 3 Pebble Hollow Court, The Woodlands, TX 77381 (US). (74) Agent: UHL, Jill, E.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606-6402 (US).</p>	<p>(81) Designated States: AU, BR, CA, CN, ES, IL, JP, KR, MX, NO, NZ, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: METHODS FOR MODULATING THE HUMAN SEXUAL RESPONSE</p>		
<p>(57) Abstract</p> <p>This invention is directed to improved methods for modulating the human sexual response by administering a vasodilator to the circulation through transmucosal, including but not limited to, administration through the vaginal mucosa, transdermal, intranasal or rectal routes of administration.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

METHODS FOR MODULATING THE HUMAN SEXUAL RESPONSE

FIELD OF THE INVENTION

5 The application is directed to improved methods for modulating the human sexual response by administering vasodilator agents to the circulation of a human via transmucosal, including but not limited to, administration through the vaginal mucosa, transdermal, intranasal or rectal routes of administration.

BACKGROUND OF THE INVENTION

10 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.

15 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
20 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
25 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

- 2 -

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 because 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

- 3 -

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, 5 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.

10 U.S. Patent No. 4,127,118 to Latorre describes treating male impotence by directly injecting 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 15 sympathomimetic amines such as nylidrin hydrochloride, adrenergic blocking agents such as tolazoline hydrochloride, and direct acting vasodilators such as isoxsuprine hydrochloride and nicotiny alcohol.

Brindley, G.S. (*Br. J. Pharmac.* **87**:495-500 1986) showed that, when injected directly into the corpus cavernosum using a 20 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 25 other drugs studied induced erections lasting from about 11 minutes to about 6.5 hours. Zorogniotti *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 30 that intracavernosal injection of papaverine hydrochloride and

- 4 -

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.

- 5 -

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.

5 Of interest to the background of the invention are the disclosures of Stanley *et al.*, U.S. Patent No. 4,885,173, which addresses methods for non-invasively 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
10 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, calcium channel blockers, β -adrenergic blocking agents, serotonin receptor blocking agents, angina blocking agents, other anti-hypertensive agents, cardiac stimulating
15 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.

20 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
25 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.

SUMMARY OF THE INVENTION

The present invention provides improved methods for modulating the human sexual response 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 by a route selected from the group consisting of transmucosal, including vaginal mucosal, transdermal, intranasal and rectal. Vasodilating agents useful in the present invention include, but are not limited to, the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, apomorphine, phenoxybenzamine, yohimbine, organic nitrates (e.g. nitroglycerin), thymoxamine, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline and papaverine. The presently preferred agent is phentolamine mesylate. The presently preferred administrative route is transmucosal, especially through the vaginal mucosa.

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 administering the agent by an administrative route selected from the group consisting of transmucosal, transdermal, intranasal, and rectal.

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 transmucosal, including vaginal mucosal, transdermal, intranasal, or rectal administration of an effective amount of vasodilator agent. A preferred form of transmucosal administration in the

- 7 -

female is by addition of an effective amount of the vasodilating agent to vaginal suppository formulations well known in the art.

Other preferred embodiments include, but are not limited to, improving the female sexual response by administration of an effective amount of the vasodilating agent. The vasodilating agent can be administered transmucosally using creams, gels, tablet inserts and solution formulations.

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 transmucosal, including vaginal mucosal, transdermal, intranasal, and rectal administration to modulate sexual response in a human. 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

- 8 -

females is result of engorgement of the erectile tissues of the genitalia with blood in response to sexual stimulation (physical, psychological, or both).

5 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
10 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
15 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.

20 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 arteria dorsalis clitoridis in the female, while the artery of
25 the corpus cavernosum in the male is analogous to the artery of the same name in the female.

30 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

- 9 -

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)].

- 10 -

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.

5 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
10 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
15 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
20 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.

 As many as half the cases of male impotence may be psychogenic because there is no readily-ascertainable organic cause for
25 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 using vasoactive agents administered to the circulation by a route selected from the group consisting of
30 transmucosal, including vaginal mucosal, transdermal, intranasal, and rectal.

- 11 -

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, phentolamine hydrochloride, phentolamine mesylate, apomorphine, 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 nicotiny 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.

In the practice of the present invention, vasoactive agents are administered by the transmucosal, including vaginal mucosal, intranasal, transdermal, or rectal routes of administration such that the agent is conveyed in circulation to the site of action prior to entering portal circulation.

- 12 -

Oral administration of a drug in an attempt to effect delivery to a specific site within circulation may have several drawbacks. First, drug absorption is limited by gastrointestinal transit time and thus, the rapidity of onset of drug action may be limited. Second, the drug may be inactivated (e.g. by hydrolysis) in the low pH environment of the stomach and or by other chemical or biochemical interactions in the intestines.

Transmucosal, including vaginal mucosal, transdermal, intranasal, and rectal routes of administration of vasodilators according to the present invention allows administration of the vasodilator a short time prior to the projected initiation of intercourse ("on demand") and eliminating the need for repeated administration of the drug. Methods of the present invention are thus more convenient and help minimize any side-effects that can 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 intracavernosal injection of vasodilators.

Formulations for effecting transmucosal delivery of vasodilators according to the present invention are well known in the art. For purposes of the present invention, "transmucosal delivery" generally refers to delivery of the drug to the vaginal mucosa, the oral or pharyngeal mucosa and includes buccal delivery, sublingual delivery, and delivery to the pharyngeal mucosa, but not to the stomach. Buccal delivery may be accomplished by preparing a tablet or lozenge comprising, for example, compressed lactose and an effective amount of one or more vasodilators. Other suitable tablet compositions include, but are not limited to, a combination of an effective dose of a vasodilator, and carrier substances, tablet-binding compounds and flavoring agents such as those described in U.S. Patent No. 3,943,246 to Stürmer, which is incorporated herein by reference. Vasoactive agents may also be compounded with a variety of pharmaceutical excipients including binders

- 13 -

such as gelatin and/or corn starch or pharmaceutically acceptable gums such as gum tragacanth. Vasoactive agents may also be combined in a hard candy (which may be dissolved in the mouth) or in a chewing gum, to provide buccal or sublingual delivery to the oral mucosa.

5 Vasodilators may also be administered transmucosally by impregnating a filter paper strip or a filter paper disc with an effective amount of a vasodilator. The filter paper strip or disc may then be placed between the cheek and gum (buccally) for delivery to the vasculature. Other transmucosal delivery systems such as lollipops (as described in
10 U.S. Patent No. 4,885,173 to Stanley) or vaginal suppositories are well known in the art and are expected to be useful in the practice of the present invention.

Transdermal delivery systems are well known in the art and involve what are sometimes referred to as transdermal "patches".
15 Exemplary transdermal patches typically comprise: (1) a impermeable backing layer which may be made up of any of a wide variety of plastics or resins, e.g. aluminized polyester or polyester alone or other impermeable films; and (2) a drug reservoir comprising, for example, a vasodilator in combination with mineral oil, polyisobutylene, and alcohols gelled with USP hydroxymethylcellulose. Other exemplary drug reservoir
20 layers may comprise, for example, acrylic-based polymer adhesives with resinous cross-linking agents which provide for diffusion of the drug from the reservoir to the surface of the skin. The transdermal patch may also have a delivery rate-controlling membrane such as a microporous polypropylene disposed between the reservoir and the skin. Ethylene-
25 vinyl acetate copolymers and other microporous membranes may also be used. Typically, an adhesive layer is provided which may comprise an adhesive formulation such as mineral oil and polyisobutylene combined with the vasoactive agent.

30 Other typical transdermal patches may comprise three layers: (1) an outer layer comprising a laminated polyester film; (2) a

- 14 -

middle layer containing a rate-controlling adhesive, a structural non-woven material and the vasodilator; and (3) a disposable liner that must be removed prior to use. Transdermal delivery systems may also involve incorporation of highly lipid soluble carrier compounds such as dimethyl sulfoxide (DMSO), to facilitate penetration of the skin. Other exemplary carriers include lanolin and glycerin.

Vasodilating drugs for use in transmucosal, including vaginal mucosal, transdermal, intranasal, or rectal delivery may be chemically modified by methods well known in the art to improve their lipid solubility and thus their ability to penetrate skin or mucosal surfaces.

Rectal and vaginal suppositories are well known in the art and also useful in the practice of the present invention. Exemplary suppositories comprise a vasodilating drug combined with glycerin, glycerol monopalmitate, glycerol, monostearate, hydrogenated palm kernel oil and fatty acids. Another exemplary suppository formulation includes ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter in combination with an effective amount of a vasodilating drugs.

The present invention is also directed to the use of nasal sprays for the administration of the vasodilators. Exemplary nasal spray formulations comprise a solution of vasodilating drug in physiologic saline or other pharmaceutically suitable carrier liquids. Nasal spray compression pumps are also well known in the art and can be calibrated to deliver a predetermined dose of the vasodilator solution.

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. The invention is illustrated in the following examples with reference to phentolamine as a vasodilator and in particular, with reference to phentolamine mesylate.

Phentolamine can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water,

- 15 -

ethanol and the like are equivalent to the unsolvated forms for purposes of the invention. Phentolamine can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydroamic acids such as hydrochloric and hydrobromic; 5 as well as other acids such as sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, toluenesulfonic, and other mineral and carboxylic acids known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a 10 salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as 15 solubility in polar solvents, but the salts are otherwise equivalent to their respective free base form for purposes of this invention. Phentolamine can also form crystalline polymorph forms or crystalline forms thereof using suitable or conventional crystallization procedures.

Example 1 describes the effect of transmucosally 20 administered phentolamine mesylate on penile arterial velocity. Examples 2 and 3 describe the effect of buccally administered phentolamine mesylate on erectile ability in impotent men. Example 4 describes the use of a variety of vasodilators in the practice of the present invention. Example 5 addresses practice of the present invention in 25 modulating erectile response in females.

- 16 -

EXAMPLE 1
EFFECT OF TRANSMUCOSAL ADMINISTRATION
OF PHENTOLAMINE MESYLATE ON
PENILE ARTERIAL VELOCITY

5 In order to assess whether or not buccally administered
phentolamine mesylate could alter arterial blood flow in the penis, penile
arterial velocity was measured close to the base of the right branch of the
dorsal artery of the penis by doppler ultrasound velocimetry using a
Diasonics 400 DRF (Diasonics, Milpitas, CA). Settings, incidence of
10 doppler beam, and angle correction were maintained to achieved
maximum velocity readings on each subject. The dorsal artery was
selected for measurement because it was more accessible than the
artery of the corpus cavernosum.

 Velocities were measured before the transmucosal (buccal)
15 administration of phentolamine mesylate (20 mg) and at 5, 15, 45 and 60
minutes after administration of the drug. Mean initial velocity was 10.4
cm/sec. The data shown in Figure 1 shows the percentage increase in
penile artery velocity versus time after administration of phentolamine
mesylate and represent the mean of triplicate readings in six impotent
20 subjects.

 The results show that, within five minutes of placing the
tablet between the cheek and gum, arterial velocity rose by more than
50% above base line velocity. Within 25 minutes, arterial velocity peaked
at more than 100% above base line velocity after which velocity began to
25 fall, reaching pretreatment levels after 1 hour. Buccal administration of
20 mg of phentolamine mesylate is thus shown to provide a suitable
means for rapidly altering penile arterial blood flow.

- 17 -

EXAMPLE 2
EFFECT OF TRANSMUCOSAL (BUCCAL) ADMINISTRATION OF
PHENTOLAMINE MESYLATE ON MALE ERECTILE ABILITY

The fact that buccal administration of 20 mg of
5 phentolamine mesylate as in Example 1 resulted in a rapid increase in
penile artery velocity supported utility of this route of administration of
vasodilators in improving erectile ability in impotent men. Thus, studies
were therefore conducted to determine the effect of transmucosal
administration of phentolamine mesylate on erectile ability in impotent
10 men.

All patients included in the study complained of an erectile
dysfunction which either prevented vaginal penetration or was
characterized by an inability to maintain an erection without ejaculation
upon initiation of vaginal penetration. The duration of impotence was
15 within a range of 0.5 years to 35 years in this patient population and the
mean duration was 3.4 years.

Prior to administration of phentolamine mesylate or placebo,
a medical history was taken, a genital examination was performed, and
penile vascular status was determined. Vascular status was determined
20 by measuring brachial and penile systolic closing pressures and
calculating a penile brachial index (PBI). PBI was calculated by dividing
the penile systolic pressure by the brachial systolic pressure.
Plethysmographic crest times (CT) were measured with a Penilab IV
plethysmograph (Parkes, Aloha WA). Crest time is the time in seconds
25 from the trough of the penile blood pressure curve to the next peak. The
normal range of crest times is from about 1 second to about 1.8 seconds.
A PBI of >0.9 is considered normal while a PBI of <0.6 indicates vascular
insufficiency.

For the purposes of this study, the patients were identified
30 as having normal vascularity if both PBI and CT were in the normal range.

- 18 -

Patients having both CT and PBI in the abnormal range were identified as having marked vascular insufficiency. Patients having one parameter in the abnormal range were identified as having moderate vascular insufficiency.

5 Age and diagnosis were generally not a factor in admission to the study, although patients with extreme age or severe penile vascular insufficiency were excluded. Patients having vascular or non-specific causes of impotence were admitted to the trial, as were patients having diabetes mellitus. Mean age of patients was 57.5 years (range: 25-74
10 years).

 In order to test the effort of phentolamine mesylate on erectile ability, a single blind trial was conducted. Each patient was given two tablets; a placebo tablet comprising lactose alone, and a second lactose tablet containing 20 mg of phentolamine mesylate.

15 Patients were asked to place one tablet between the cheek and gum (buccal) 10-20 minutes before attempting coitus. Buccal administration was used as a paradigm of transmucosal delivery which, like all routes of delivery useful in the practice of the present invention, results in the drug reaching the vasculature of the target (genitalia) prior
20 to passing through the liver. One or more days after using the first tablet, patients repeated the process with the second tablet. Patients were advised not to swallow the tablets or 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
25 and were told to report results in terms of erection and vaginal penetration, partial erection, or failure to maintain an erection sufficient to permit vaginal penetration. Patients were also asked to report side effects. Results of this study are illustrated in Table 1 which shows the age, vascular status and effect of phentolamine mesylate on erectile
30 ability in impotent men. In the right-hand columns of Table 1, the number 1 indicates a report of erection and vaginal penetration, 2 indicates

- 19 -

reported failure to achieve erection, and 3 indicates report of a partial erection.

TABLE 1
 VASCULAR STATUS AND THE EFFECTS OF BUCCAL ADMINISTRATION
 OF PHENTOLAMINE ON PENILE ERECTILE ABILITY IN IMPOTENT MEN

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
1	60	1.5	0.75	0.87	3	2
2	60	2.4	0.79	0.82	1	2
3	64	2.4	0.78	0.81	1	2
4	61	2.4	0.72	0.72	2	2
5	60	2.2	0.84	0.82	1	2
6	39	1.4	0.77	0.79	1	1
7	46	1.6	0.91	1.00	2	2
8	33	1.4	0.76	0.78	3	2
9	44	1.6	0.99	0.89	2	2
10	36	2.4	0.90	0.90	2	2
11	66	2.2	0.91	0.90	1	2
12	45	1.8	0.67	0.87	1	1

5

10

15

TABLE I cont'd.

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
13	50	2.0	0.81	0.74	2	2
14	62	1.6	0.82	0.97	3	2
15	51	1.8	0.78	0.89	3	2
16	44	2.6	0.69	0.69	1	1
17	38	2.0	1.00	0.87	2	2
18	49	1.4	0.93	0.94	1	2
19	49	2.2	0.89	1.04	2	2
20	53	2.4	0.80	0.86	2	2
21	65	1.6	1.05	0.96	1	2
22	54	1.6	0.80	0.81	2	1
23	65	1.8	0.95	0.93	1	1
24	63	1.6	1.00	0.99	2	1
25	64	2.0	0.86	0.77	3	2
26	54	1.2	0.92	0.88	1	2

TABLE 1 cont'd.

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
27	65	2.6	0.98	0.93	2	2
28	64	2.8	0.90	0.80	2	2
29	67	2.4	0.84	0.89	2	2
30	68	2.2	0.74	0.71	1	2
31	60	2.0	1.03	1.00	2	2
32	51	1.6	0.79	0.75	2	2
33	72	2.8	1.05	1.07	1	1
34	59	2.4	0.55	0.56	1	2
35	56	1.6	0.68	0.79	1	2
36	59	2.4	0.85	0.79	2	2
37	58	3.2	0.65	0.53	2	1
38	50	2.2	0.89	0.98	2	2
39	66	2.4	0.59	0.54	1	3
40	51	2.8	0.66	0.55	3	2

TABLE 1 cont'd.

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
41	53	2.8	0.69	0.78	2	2
42	62	2.2	0.93	0.95	2	2
43	66	2.0	0.80	0.82	1	1
44	56	2.0	0.65	0.73	3	2
45	74	2.9	0.86	0.87	2	2
46	63	2.2	1.10	1.08	2	2
47	72	2.0	0.55	0.67	2	2
48	70	2.4	0.81	0.83	2	2
49	69	2.4	0.95	0.95	2	2
50	55	2.0	0.82	0.80	3	2
51	55	2.4	1.01	0.92	2	3
52	65	2.4	0.81	0.80	3	2
53	60	2.0	0.74	0.83	2	2
54	62	1.6	0.87	0.88	1	2

TABLE 1 cont'd.

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
55	53	2.2	1.02	0.98	2	2
56	37	1.6	0.96	0.87	1	2
57	55	2.0	0.71	0.56	1	2
58	25	1.8	0.89	0.91	2	2
59	51	2.0	1.02	1.14	2	2
60	35	2.0	0.85	0.98	2	2
61	69	2.8	0.93	0.97	2	2
62	40	2.3	0.95	0.91	2	2
63	54	2.0	0.98	0.86	1	2
64	76	2.2	0.70	0.71	3	2
65	53	2.4	0.92	0.90	2	2
66	59	2.6	0.79	0.69	2	2
67	59	2.0	0.83	0.87	2	2
68	53	3.2	0.58	0.78	1	2

TABLE 1 cont'd.

Patient Number	Age	Crest Time	Penile Brachial Indices		Phentolamine (20 mg)	Placebo
			Right	Left		
69	38	2.2	0.88	0.85	2	2

- 26 -

The data in Table 1 illustrates that buccal administration of 20 mg of phentolamine mesylate resulted in improved erectile ability within 10 minutes to 20 minutes after buccal administration of the drug.

The response was characterized by improved erectile ability upon sexual stimulation and thus, the response closely mimicked the normal sexual response in men. The fact that the effect of the drug was seen within 10-20 minutes after a single administration can be characterized as a response occurring "on demand" in that multiple doses and/or a long waiting time before onset of improved erectile ability were not required.

5

10 The rapid increase in penile artery velocity within five minutes of administration of phentolamine mesylate (as indicated in Example 1) suggests that improve erectile ability may actually occur sooner than 10 minutes after administration. The "on demand" aspect of the method of the present invention allows a more natural and more spontaneous approach to intercourse and eliminates the need for multiple doses, and thus, reduces the frequency of undesirable side effects. Although a 20 mg dose of phentolamine mesylate was used in the present study, doses from about 5 mg to about 80 mg of phentolamine mesylate are within the scope of the present invention as individual responsiveness to the drug may vary *e.g.*, on the basis of total body weight and degree of vascular insufficiency.

15

20

The data set out in Table 1 was further analyzed to determine if the vascular status of the patients had any predictive value with respect to the efficacy of phentolamine mesylate in improving the erectile ability in impotent patients. The analysis showed that, of 16 total patients with normal vascular status, seven were successfully treated with phentolamine mesylate, six failed to respond, and three achieved partial erection. Of the 49 patients with vascular insufficiency, 15 were successful in achieving erection sufficient for vaginal penetration, while 29 failed. Five patients with vascular insufficiency achieved partial erection. The side effects seen in this study were infrequent and include,

25

30

- 27 -

stuffy nose (6%), faintness or dizziness (2.3%) (relieved by lying down for 10-15 minutes) and vomiting 0.05%.

EXAMPLE 3
EFFECT OF BUCCAL PHENTOLAMINE MESYLATE AND
IMPOTENCE OF VARIOUS ETIOLOGIES

5

Another single blind study was conducted in men having erectile dysfunction of various etiologies in order to further assess the efficacy of buccally administered phentolamine in ameliorating erectile dysfunction.

10

A mixed population of men having erectile dysfunction of various etiologies were given 3 filter paper strips impregnated with 20 mg of phentolamine mesylate and 3 placebo strips. The patients were not told which strips contained the drug and which strips were placebo. Patients were told to place one filter paper strip between the cheek and gum 10 minutes to 20 minutes prior to attempts to achieve erection. The treatment was deemed successful if an erection sufficient to affect vaginal penetration was achieved. The results are shown in Table 2.

15

TABLE 2

Patient No.	Etiology	Result
1	Peyronie's Disease and associated erectile dysfunction	2
2	psychogenic	1
3	arteriogenic/psychogenic	1
4	neurogenic	2
5	arteriogenic	1
6	arteriogenic	1
7	*	2
8	*	2
9	*	2
10	*	2
11	*	2
12	psychogenic	No Report
13	arteriogenic	1
14	psychogenic	1
15	arteriogenic	2
16	psychogenic	1
17	psychogenic	1
18	arteriogenic/psychogenic	1
19	arteriogenic	2
20	psychogenic	1
21	arteriogenic	2
22	arteriogenic	2
23	arteriogenic/psychogenic	2

TABLE 2 cont'd

*
5 Prior to enrolling in this study, patients Nos. 7-11 were on a program of intracavernosal auto-injection using 20µg of PGE-1 with perfect efficacy. These patients also suffered from severe cardiovascular disease.

1 = erection and vaginal penetration

2 = failure to achieve erection sufficient for vaginal penetration

The results of this study establish that buccally administered phentolamine mesylate (20 mg) improved erectile ability in 36% of the
10 patients reporting (excluding a total of two placebo responders). The results were most pronounced in patients with a diagnosis of psychogenic impotence wherein 5 of 5 patients reporting achieved an erection sufficient to vaginal penetration. Of those patients diagnosed as having arteriogenic impotence 3 of 7 patients showed improved erectile ability,
15 with one of these patients also responding to placebo. Two of three patients diagnosed as having combined arteriogenic/psychogenic impotence showed improved erectile ability, with one of these patients also responding to placebo. Of the 5 patients in whom autoinjection of PGE-1 had shown perfect efficacy, none showed improvement in erectile
20 ability with buccally administered phentolamine mesylate.

These results, when combined with those set out in Example 2, indicate that vasodilators such as phentolamine mesylate when administered via a transmucosal route of administration is effective in improving the onset of erectile ability in a significant percentage of
25 impotent men and more particularly in men having psychogenic, arteriogenic, or combined psychogenic/arteriogenic impotence, the subpopulation of patients comprising the majority of cases of male impotence.

- 30 -

While useful in the treatment of impotence in males, the present invention is also useful in improving erectile ability in non-impotent men. It is well known that as men age, erectile ability may be altered. One manifestation of this decline in erectile ability is that the angle of erection subtended by the dorsal surface of the erect penis and the abdomen (erectile angles) increases with age. The method of the present invention, provides a means for improving erectile ability in non-impotent men by increasing blood flow to the penis, and thereby minimizing the erectile angle.

It should also be noted that filter strips impregnated with phentolamine mesylate lost their potency after several months of storage at room temperature in a paper bag.

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.

- 31 -

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.

5 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.

10 In the practice of the present invention, these vasoactive agents are administered by the transmucosal, including vaginal mucosal, intranasal, transdermal, or rectal routes of administration such that the agent reaches its site of action prior to entering the portal circulation.

 Appropriate doses of each vasoactive agents for each route
15 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
20 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
25 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.

30 Yohimbine hydrochloride available as Daytohimbin® (Dayton Pharmaceuticals), Yocon® (Palisades Pharmaceuticals), and

- 32 -

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
5 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
10 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 Example 1. Other methods such as thermography, plethysmography, radiometric or scintigraphic methods, and other methods well known in the art may also be utilized to assess
15 blood flow in the genitalia. Having established base line blood flow, various dosages of the respective vasodilators may be administered by the routes of administration 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
20 response in humans may vary from individual to individual, but is readily determined as described below. 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
25 assessments of sexual responsiveness as evidenced by the improvement of erectile ability in response to sexual stimulation.

- 33 -

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
5 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 of the present invention may be used to
10 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
15 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
20 heightened sensation associated with excitement and plateau stages of the female sexual response by virtue of the increased blood flow to the genitalia.

In practice, enhancement of the female sexual response using the methods of the present invention are carried out in much the
25 same way as those described in Examples 2 and 3.

An effective vasodilating dose of a vasodilating agent is administered to a woman via the transmucosal, including but not limited to, through the vaginal mucosa, transdermal, intranasal, or rectal routes of administration. The appropriate doses of the particular vasodilating
30 agent may be readily determined using methods described in Example 4.

- 34 -

Exemplary vasodilators useful in the practice of the present invention are set out in Example 4 and include those generally classified as α -adrenergic antagonists, sympathomimetic amines and those agents which exhibit direct relaxation of vascular smooth muscle. The female
5 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,
10 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
15 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
20 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.

A preferred embodiment of the present invention involves the transmucosal administration of from about 5 mg to about 150 mg of
25 phentolamine mesylate, preferably from about 15 mg to about 100 mg of phentolamine mesylate, more preferably from about 25 mg to about 80 mg of phentolamine mesylate, and most preferably 40 mg of phentolamine mesylate from about 1 minute to about 1 hour prior to, and in preparation for, intercourse. Preferably, the amount of vasodilating
30 agent used in the practice of the invention for the improvement of the female sexual response is effective to improve sexual response from

- 35 -

about 1 minute to about 1 hour after administration. More preferably, the amount of vasodilating agent used is effective to improve female sexual response from about 5 minutes to about 45 minutes after administration. It is also preferable that the amount of vasodilating agent used is effective
5 to improve female sexual response from about 15 minutes to about 30 minutes after administration. Other vasodilating agents and other routes of administration included within the scope of the present invention are also contemplated.

A presently preferred method of transmucosal
10 administration is by vaginal suppositories. Vaginal suppositories are well known in the art and are available in a variety of physical forms. Most commonly known are suppositories or pessaries which are globular or oviform and weigh about 5 g each. More recently, creams, gels or liquids which depart from the classical concept of suppositories have become
15 available and are useful in the practice of the present invention. Compositions for vaginal administration can also be supplied as vaginal tablets, or inserts prepared by encapsulation in soft gelatin. Additionally, compositions for vaginal administration can be prepared as solutions which are then lyophilized. When water is added to the lyophilized
20 solutions before administration, lyophilized solutions provide an effective means of administration. All of these physical forms are contemplated.

An exemplary vaginal suppository contains a mixture of approximately 86% polyethylene glycol 1000 NF, 10% polyethylene glycol 3350 NF and 4% phentolamine mesylate. The resulting vaginal
25 suppository provides an effective vehicle for delivering a dose of phentolamine mesylate through the vaginal mucosa.

An exemplary 40 mg phentolamine mesylate tablet insert contains a mixture of approximately 61% microcrystalline cellulose, NF; 30% hydrogenated vegetable oil, NF; 4% croscarmellose sodium, NF; 4%
30 phentolamine mesylate; 0.5% magnesium stearate, NF; and, .04% colloidal silicon dioxide. The mixture is pressed into a tablet form and the

- 36 -

resulting tablet inserts are then encapsulated in soft gelatin by methods commonly known in the art. The encapsulated insert is then administered to a woman through the vaginal mucosa.

5 An exemplary vaginal gel for administration of the present invention includes a mixture of approximately 75% water, 15% glycerin, 7% phentolamine mesylate and less than 1% hydroxyethylcellulose, methylparaben and glucono- δ -lactone. The resulting vaginal gel provides an effective vehicle for delivering a dose of phentolamine mesylate through the vaginal mucosa.

10 An exemplary solution for lyophilization includes phentolamine mesylate, citric acid, sodium bicarbonate, mannitol, and magnesium stearate. After lyophilization, water was added to re-hydrate before administering to a woman through the vaginal mucosa.

15 Another exemplary solution comprises a mixture of approximately 83% potable water, 13% phentolamine mesylate and 4% D-mannitol. The resulting solution provides another effective vehicle for delivering a dose of phentolamine mesylate through the vaginal mucosa.

Additional suppository, gel, cream, solution or insert formulations are also included within the scope of the present invention.

20 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 the transmucosal, including vaginal
25 mucosal, transdermal, intranasal, or rectal routes of administration.

- 37 -

We Claim:

1. In a method for modulating sexual response in a human by administering a vasodilator agent to blood circulation in an amount effective to increase blood flow to the genitalia, the improvement comprising modulating the sexual response on demand by transmucosal administration of an effective amount of the agent.

2. The improvement of claim 1 wherein the vasodilating agent is selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, apomorphine, phenoxybenzamine, nitroglycerin, thymoxamine, nicotiny alcohol, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine.

3. The improvement of claim 1 or 2 wherein the route of administration is through the vaginal mucosa.

4. The improvement of claim 1 or 2 wherein the agent administered is selected from the group consisting of phentolamine, phentolamine mesylate and phentolamine hydrochloride.

5. The improvement of claim 3 wherein the agent administered is selected from the group consisting of phentolamine, phentolamine mesylate and phentolamine hydrochloride.

6. The improvement of claim 4 wherein the amount administered is from about 5 mg to about 150 mg.

7. The improvement of claim 5 wherein the amount administered is from about 5 mg to about 150 mg.

- 38 -

8. The improvement of claim 4 wherein the amount administered is from about 15 mg to about 100 mg.

9. The improvement of claim 5 wherein the amount administered is from about 15 mg to about 100 mg.

10. The improvement of claim 4 wherein the amount administered is from about 25 mg to about 80 mg.

11. The improvement of claim 5 wherein the amount administered is from about 25 mg to about 80 mg.

12. The improvement of claim 4 wherein the amount administered is 40 mg.

13. The improvement of claim 5 wherein the amount administered is 40 mg.

14. The improvement of any one of claim 1, 2 and 5-13 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

15. The improvement of claim 3 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

16. The improvement of claim 4 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

- 39 -

17. The improvement of any one of claim 1, 2 and 5-13 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

18. The improvement of claim 3 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

19. The improvement of claim 4 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

20. The improvement of any one of claim 1, 2 and 5-13 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

21. The improvement of claim 3 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

22. The improvement of claim 4 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

23. The improvement of any one of claims 5-13, 15, 16, 18, 19, 21 or 22 wherein the administration is in the form of a vaginal suppository.

- 40 -

24. The improvement of claim 3 wherein the administration is in the form of a vaginal suppository.

25. The improvement of claim 4 wherein the administration is in the form of a vaginal suppository.

26. The improvement of claim 14 wherein the administration is in the form of a vaginal suppository.

27. The improvement of claim 17 wherein the administration is in the form of a vaginal suppository.

28. The improvement of claim 20 wherein the administration is in the form of a vaginal suppository.

29. The improvement of any one of claims 5-13, 15, 16, 18, 19, 21 or 22 wherein the administration is in the form of a tablet insert.

30. The improvement of claim 3 wherein the administration is in the form of a tablet insert.

31. The improvement of claim 4 wherein the administration is in the form of a tablet insert.

32. The improvement of claim 14 wherein the administration is in the form of a tablet insert.

33. The improvement of claim 17 wherein the administration is in the form of a tablet insert.

- 41 -

34. The improvement of claim 20 wherein the administration is in the form of a tablet insert.

35. The improvement of any one of claims 5-13, 15, 16, 18, 19, 21 or 22 wherein the administration is in the form of a re-hydrated lyophilized solution.

36. The improvement of claim 3 wherein the administration is in the form of a re-hydrated lyophilized solution.

37. The improvement of claim 4 wherein the administration is in the form of a re-hydrated lyophilized solution.

38. The improvement of claim 14 wherein the administration is in the form of a re-hydrated lyophilized solution.

39. The improvement of claim 17 wherein the administration is in the form of a re-hydrated lyophilized solution.

40. The improvement of claim 20 wherein the administration is in the form of a re-hydrated lyophilized solution.

41. The improvement of any one of claims 5-13, 15, 16, 18, 19, 21 or 22 wherein the administration is in the form of a vaginal gel or cream.

42. The improvement of claim 3 wherein the administration is in the form of a vaginal gel or cream.

43. The improvement of claim 4 wherein the administration is in the form of a vaginal gel or cream.

- 42 -

44. The improvement of claim 14 wherein the administration is in the form of a vaginal gel or cream.

45. The improvement of claim 17 wherein the administration is in the form of a vaginal gel or cream.

46. The improvement of claim 20 wherein the administration is in the form of a vaginal gel or cream.

47. The improvement of claim 41 wherein the gel comprises from about 30 mg to about 50 mg of phentolamine mesylate.

48. The improvement of any one of claims 42-46 wherein the gel comprises from about 30 mg to about 50 mg of phentolamine mesylate.

49. The improvement of claim 47 wherein the gel comprises 40 mg of phentolamine mesylate.

50. The improvement of claim 48 wherein the gel comprises 40 mg of phentolamine mesylate.

51. A method for the manufacture of a medicament for modulating sexual response in a human by administering a vasodilator agent to blood circulation in an amount effective to increase blood flow to the genitalia, said method comprising modulating the sexual response on demand by transmucosal administration of an effective amount of the agent.

- 43 -

52. The method of claim 18 wherein the vasodilating agent is selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, apomorphine, phenoxybenzamine, nitroglycerin, thymoxamine, nicotiny alcohol, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine.

53. The method of claim 51 or 52 wherein the route of administration is through the vaginal mucosa.

54. The method of claim 51 or 52 wherein the agent administered is selected from the group consisting of phentolamine, phentolamine mesylate and phentolamine hydrochloride.

55. The method of claim 53 wherein the agent administered is selected from the group consisting of phentolamine, phentolamine mesylate and phentolamine hydrochloride.

56. The method of claim 54 wherein the amount administered is from about 5 mg to about 150 mg.

57. The method of claim 55 wherein the amount administered is from about 5 mg to about 150 mg.

58. The method of claim 54 wherein the amount administered is from about 15 mg to about 100 mg.

59. The method of claim 55 wherein the amount administered is from about 15 mg to about 100 mg.

- 44 -

60. The method of claim 54 wherein the amount administered is from about 25 mg to about 80 mg.

61. The method of claim 55 wherein the amount administered is from about 25 mg to about 80 mg.

62. The method of claim 54 wherein the amount administered is 40 mg.

63. The method of claim 55 wherein the amount administered is 40 mg.

64. The method of any one of claim 51, 52 and 55-63 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

65. The method of claim 53 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

66. The method of claim 54 wherein the amount administered is effective to improve the female sexual response within about 1 minute to about 1 hour after administration.

67. The method of any one of claim 51, 52 and 55-63 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

- 45 -

68. The method of claim 53 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

69. The method of claim 54 wherein the amount administered is effective to improve the female sexual response within about 5 minutes to about 45 minutes after administration.

70. The method of any one of claim 51, 52 and 55-63 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

71. The method of claim 53 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

72. The method of claim 54 wherein the amount administered is effective to improve the female sexual response within about 15 minutes to about 30 minutes after administration.

73. The method of any one of claims 55-63, 65, 66, 68, 69, 71 or 72 wherein the administration is in the form of a vaginal suppository.

74. The method of claim 53 wherein the administration is in the form of a vaginal suppository.

75. The method of claim 54 wherein the administration is in the form of a vaginal suppository.

- 46 -

76. The method of claim 64 wherein the administration is in the form of a vaginal suppository.

77. The method of claim 67 wherein the administration is in the form of a vaginal suppository.

78. The method of claim 70 wherein the administration is in the form of a vaginal suppository.

79. The method of any one of claims 55-63, 65, 66, 68, 69, 71 or 72 wherein the administration is in the form of a tablet insert.

80. The method of claim 53 wherein the administration is in the form of a tablet insert.

81. The method of claim 54 wherein the administration is in the form of a tablet insert.

82. The method of claim 64 wherein the administration is in the form of a tablet insert.

83. The method of claim 67 wherein the administration is in the form of a tablet insert.

84. The method of claim 70 wherein the administration is in the form of a tablet insert.

85. The method of any one of claims 55-63, 65, 66, 68, 69, 71 or 72 wherein the administration is in the form of a re-hydrated lyophilized solution.

- 47 -

86. The method of claim 53 wherein the administration is in the form of a re-hydrated lyophilized solution.

87. The method of claim 54 wherein the administration is in the form of a re-hydrated lyophilized solution.

88. The method of claim 64 wherein the administration is in the form of a re-hydrated lyophilized solution.

89. The method of claim 67 wherein the administration is in the form of a re-hydrated lyophilized solution.

90. The method of claim 70 wherein the administration is in the form of a re-hydrated lyophilized solution.

91. The method of any one of claims 55-63, 65, 66, 68, 69, 71 or 72 wherein the administration is in the form of a vaginal gel or cream.

92. The method of claim 53 wherein the administration is in the form of a vaginal gel or cream.

93. The method of claim 54 wherein the administration is in the form of a vaginal gel or cream.

94. The method of claim 64 wherein the administration is in the form of a vaginal gel or cream.

95. The method of claim 67 wherein the administration is in the form of a vaginal gel or cream.

- 48 -

96. The method of claim 70 wherein the administration is in the form of a vaginal gel or cream.

97. The method of claim 91 wherein the gel comprises from about 30 mg to about 50 mg of phentolamine mesylate.

98. The method of any one of claims 92-96 wherein the gel comprises from about 30 mg to about 50 mg of phentolamine mesylate.

99. The method of claim 97 wherein the gel comprises 40 mg of phentolamine mesylate.

100. The method of claim 98 wherein the gel comprises 40 mg of phentolamine mesylate.