(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2010 (22.04.2010)

PCT

(10) International Publication Number
WO 2010/044094 A2

(51) International Patent Classification:
*A61K 31/4162* (2006.01) *A61P 9/12* (2006.01)
*A61K 31/519* (2006.01) *A61P 15/10* (2006.01)
*A61K 31/10* (2006.01)

(21) International Application Number:
PCT/IN2009/000484

(22) International Filing Date:
3 September 2009 (03.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1178/MUM/2008 3 September 2008 (03.09.2008) IN

(72) Inventors; and
(71) Applicants : **AGARWAL, Krishna, Radharaman** [IN/IN]; 172 Kalpataru Habitat, Dr.S.S. Road, Parel, Mumbai 400 012, Maharashtra (IN). **GARG, Sanjiv, Surajbhan** [IN/IN]; 10/C Sagar Sangeet, 58-Colaba Road, Mumbai 400 005, Maharashtra (IN).

(74) Agent: **KHADILKAR, Murlidhar, Shrikrishna**; 702, Rehman House, 18/A, Nadirsha Sukhia Street, Behind Prospect Chambers, Fort, Mumbai 400 001 Maharashtra (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *of inventorship (Rule 4.17(iv))*

**Published**:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2010/044094 A2

(54) Title: A TOPICAL COMPOSITION FOR THE TREATMENT OF ERECTILE DYSFUNCTION

(57) Abstract: A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) comprising pharmaceutically effective amount of l-[[3-(6,7- dihydro-l-methyl-7-oxo-3-propyl-IH-pyrazolo[4,3-pyrimidin-5-yl)-4 ethoxyphenyl] sulfonyl] -4-methyl piperazine citrate and desensitizing agent along with pharmaceutically acceptable excipients.

**TITLE**

A TOPICAL COMPOSITION FOR THE TREATMENT OF ERECTILE DYSFUNCTION.

**FIELD OF THE INVENTION;**

The field of invention relates to topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH). The field of invention particularly relates to topical composition for local administration of drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH).

The field of invention more particularly relates to the topical composition for local administration of combination of Sildenafil citrate and Lidocaine.

**BACKGROUND OF THE INVENTION;**

Erectile dysfunction refers to a condition of the inability to achieve and maintain penile erection sufficient to complete satisfactory sexual intercourse. There are two major causes for the erectile dysfunction: psychogenic and organic causes. Previously, erectile dysfunction was thought to be of psychogenic origin. In these days, however, it is believed that most of erectile dysfunction comes from organic causes resulting from damage in nerve, blood vessel or hormone system, surgery, or drug administration.

Erectile dysfunction can be cured with surgical or pharmacological means, for the pharmacological treatment, some effective drugs are available, orally or locally.

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP)- specific phosphodiesterase type 5 (PDE5), Sildenafil citrate is designated chemically as l-[[3-(6,7-dihydro-l-methyl-7- oxo-3-propyl-lH-pyrazolo[4,3-^pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl piperazine citrate,

United States Patent 6,156,753 teaches about the local administration of type III phosphodiesterase inhibitors for the treatment of erectile dysfunction.The method involves the administration of a Type III phosphodiesterase inhibitor or a pharmaceutically acceptable salt, ester, amide or derivative thereof, wherein administration is transurethral, topical or transdermal.

United States Patent 6,127,363 provides a method for treating erectile dysfunction, e.g., vasculogenic erectile dysfunction such as vasculogenic impotence. The method involves the administration of a Type IV phosphodiesterase inhibitor or a pharmaceutically acceptable salt, ester, amide or derivative thereof, wherein administration is local, i.e., transurethral, intracavernosal, topical or transdermal. A preferred mode of administration is transurethral. Pharmaceutical formulations and kits are provided as well.

In addition it advantages to administer Sildenafil citrate locally as topical composition because it is known in the art that oral compositions are having bitter taste, hence prior art teaches taste masked compositions like recent published PCT patent application No.WO/2009/074995 the present invention relates to chewable solid pharmaceutical compositions comprising sildenafil citrate. Sildenafil citrate is a very bitter drug, hence the conventional tablets, comprise of a film coating for aesthetic appearance and acceptability. Chewable tablets are usually uncoated and hence there is a need to mask the bitter taste of sildenafil to ensure patient acceptability.

In addition other patent applications/ granted patents teaches the taste masked compositions are as follows,

U.S. Patent No. 6,197,348 describes a dosage form that utilizes encapsulated particles coated with polymers, such as Eudragit RS and Eudragit RL. Taste

masking is achieved as a result of the polymer coatings and a liquid suspending medium having a pH that is adjusted to a point where the active ingredient is insoluble. However, the thickness and type of coating is not sufficient for taste masking.

U.S. Application 2002/064563 discloses a taste masked composition of topiramate and a process for its preparation. The process includes preparing core particles which include the active ingredient topiramate, coating with a taste masked mixture to form coated particles, and drying the coated particles.

U.S. Patent No. 5,084,278 describes a chewable taste masked pharmaceutical composition having a controlled release profile. The composition comprises microcapsules with are made up of an active ingredient core coated with a polymer mixture. The coating includes a blend of ethyl cellulose and polymethacrylic acid ester copolymers. United States Patent 6,299,902 teaches a novel topical anesthetic preparation with improved transdermal absorption and efficacy, the topical preparation contains at least one local anesthetic agent and at least two melting point depressing agents. Also provided is a two-phase liquid composition that contains aqueous and oil phases, the oil phase having a relatively high concentration of a local anesthetic agent to enhance transdermal absorption and efficacy when incorporated into a topical anesthetic preparation. A topical anesthetic preparation includes lidocaine or tetracaine, thymol or menthol, and ethyl alcohol or isopropyl alcohol. The preparation is expected to be safe and effective in obtaining transdermal anesthesia on intact skin and mucous membrane.

WO1997/044021 teaches about pharmaceutical products for the relief of pain, in particular the use of novel complexes of amide-type local anesthetics, e.g.

lignocaine.

**OBJECT OF THE INVENTION;**

An object of the present invention is to prepare topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH).

Another, object of the invention is to prepare topical composition for local administration of drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH).

Yet another object of the invention is to prepare topical composition for local administration of drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH) comprising combination of Sildenafil citrate and Lidocaine.

Yet another object of the invention is to provide a method for the manufacturing of topical composition for local administration of drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH) comprising combination of Sildenafil citrate and Lidocaine.

**SUMMARY OF THE INVENTION;**

The present invention relates to topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH). The topical composition for the treatment of the erectile dysfunction and pulmonary arterial hypertension (PAH) and to prolong duration of erection by desensitizers.

The topical composition comprising -[[3-(6,7-dihydro-l-methyl-7- oxo-3-propyl-lH-pyrazolo[4,3-^pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl piperazine citrate i.e Sildenafil citrate and desensitizing agent Lidocaine. The topical composition further comprises pharmaceutically acceptable excipients.

## DEATILED DESCRIPTION OF THE INVENTION;

Erectile dysfunction refers to a condition of the inability to achieve and maintain penile erection sufficient to complete satisfactory sexual intercourse. There are two major causes for the erectile dysfunction: psychogenic and organic causes. Previously, erectile dysfunction was thought to be of psychogenic origin. In these days, however, it is believed that most of erectile dysfunction comes from organic causes resulting from damage in nerve, blood vessel or hormone system, surgery, or drug administration.

Erectile dysfunction can be cured with surgical or pharmacological means. For the pharmacological treatment, some effective drugs are available, orally or locally.

Recently, sildenafil citrate which is a selective inhibitor of phosphodiesterase has been introduced into the market as an oral drug. This new oral drug showed positive result in the treatment of erectile dysfunction. However, the oral administration of a drug accompanies systemic side effects inevitably, since the drug reaches the site of action after it is distributed throughout the whole body by the systemic circulation. Sildenafil also has some systemic side effects such as headache, flushing, indigestion and changes in vision, etc.

The oral dosage forms of the sildenafil citrate are marked with the bitter taste hence in order to overcome taste issue for the oral dosage forms , several taste masked tablets are introduced. The mechanism of action of Sildenafil citrate involves the release of nitric oxide (NO) in the corpus cavernosum of the penis. NO binds to the receptors of the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilation) of the intimal cushions of the helicine arteries,

resulting in increased inflow of blood and an erection.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil is similar to that of cGMP and acts as a competitive binding agent of PDE5 in the corpus cavernosum, resulting in more cGMP and better erections. Without sexual stimulation, and therefore lack of activation of the NO/cGMP system, sildenafil should not cause an erection.

Hence from the physiological action of the Sildenafil is responsible for the increased inflow of blood in penis and this is direct function of the bioavailability of the Sildenafil administered. High dosage of the Sildenafil causes the several side effects so it necessary to keep the dosage form as low as possible.

Sildenafil is metabolized by liver enzymes and excreted by both the liver and kidneys. If taken with a high-fat meal, absorption is reduced; the time taken to reach the maximum plasma concentration increases by around one hour, and the maximum concentration itself is decreased by nearly one-third.

According to present invention it is observed that topical composition can be suitable mode for the administration of Sildenafil. It is also possible to reduce the effective amount of the Sildenafil compared to the oral dosage forms. It is also known that oral dosage forms can leads side effects headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision. Some sildenafil users have complained of seeing everything tinted blue (cyanopsia). Some complained of blurriness and loss of peripheral vision. Another problem associated with oral dosage is the time required for achieving the desired erection which makes it practically difficult to use and there was need

for some local drug delivery system.

The Present invention solves the two problems i.e. Erectile Dysfunction(ED) and Premature Ejaculation (PE) with a single topical formulation.

It is observed that the topical composition for treatment for premature ejaculation comprises of desensitizing agent (Lidocaine) which dull the penile skin and delay ejaculation. It selectively desensitizes penile skin, affecting only the non-keratinized skin (the inner lining of the foreskin and the surface of the glans), without adversely affecting the sensation of ejaculation. It is also observed that the Topical composition prepared as per present invention is equally effective even if applied five minutes prior to intercourse and hence it solves the problem of waiting for one hour to achieve the desired Erection as necessary in the discussed prior art.

It is also advantages over the oral forms as it does not lead to the bitter taste in the mouth after administration.

According to preferred embodiment of the invention Sildenafil is combined with the Desensitization agents, which results in to prolong the erection due to the administration of the Sildenafil citrate. Desensitization is a method to reduce or eliminate an organism's negative reaction to a substance or stimulus. Though various desensitizing agents are available, the desensitization agents used in the present invention is Lidocaine / Lignocaine HCl.

According to preferred embodiment of the present invention, pharmaceutically acceptable vehicle or excipients used in the preparation of the topical composition. These excipients includes wetting agents, ionic or non-ionic surfactants polyethylene glycol surfactants including Cetomacrogol 1000,.It is used as a solubilizer and emulsifying agent in foods, cosmetics, and

pharmaceuticals, often as an ointment base, and also as a research tool. It is used as O/W emulsifier for creams/lotions; Wetting agent in sticks;

Mixture of fatty alcohols, consisting predominantly of cetyl and stearyl alcohols and is classified as a fatty alcohol including Cetostearyl alcohol, cetearyl alcohol or cetylstearyl alcohol, propylene glycol, humectants like glycerin It is used as an emulsion stabilizers ,opacaying agents, and foam boosting agent as well as an aqueous and non aqueous viscosity boosting agents. It imparts an emollient feel to the skin and can be used in water-in-oil emulsions, oil-in-water emulsions, and anhydrous formulations.

Petroleum jelly, petrolatum or soft paraffin is a semi-solid mixture of hydrocarbons (with carbon numbers mainly higher than 25), a topical ointments for its healing properties.

Preservatives in the cosmetic and pharmaceutical compositions parabens are effective preservatives including methylparaben, also methyl paraben, one of the parabens, It is the methyl ester p-hydroxy benzoic acid, Propyl paraben, Chelating agents like EDTA, solvents like demineralised water, lower alcohols C1-C3, perfumes, fragrant oils.

In another embodiment of the present invention provides a method for the preparation of the topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH). In this method the process of emulsification of the water soluble ingredients and oil vehicles takes place prior to the addition of the active agents. The method is carried in two different contains designated as "A' and 'B'. The container 'A' containing water soluble chelating agent and heated up to 80-100 $^{O}$ C. The 'B' container is containing wetting agents , ionic or non ionic surfancts, solubilizer, fatty alcohols, emulsion

stabilizers, opacaying agents, preservatives, viscosity boosting agents are homogenized at the temperature 60-90$^{O}$C to obtain the homogenized mixture, this is carried by the vacuum pressure.

The ingredients of the 'A' is mixed with 'B' are homogenized to complete the emulsification of the constituents. The homogenized constituents of the 'A' and 'B" when emulsified together results in the formation of vehicle for active agents. After completion of the emulsification process, reduce the temperature of the ingredients to 45$^{O}$C till congealing is started. Then add the previously dissolved Diazotization or local anesthetic agent such as Lidocaine HCl in water and slurry of Sildenafil Citrate with continuous stirring optionally perfume is also added with alcohol as the base at temperature of 40-50$^{O}$c. After addition of the all the constituents the mixture is stirred for 3-4 hrs. The same upon cooling to room temperature can be filled in to the tubes.

According to one of the aspect of the invention pH of the topical composition is 4.0-6.0.

**EXAMPLE;**

1. Preparation of the Container 'A' ingredients,

| Sr. | Ingredients | w/w |
|---|---|---|
| 1 | Water | 100 |
| 2 | EDTA | 10 |

The ingredients of 'A' heated up to 80$^{O}$c and allowed to cool at 60$^{O}$c.

2. Preparation of the Container 'B'in ingredients

| Sr. | Ingredients | w/w |
|---|---|---|
| 1 | Cetomacogol 1000 | 10 |
| 2 | Cetostearyl Alcohol | 10 |
| 3 | White petroleum jelly | 10 |
| 4 | Methyl paraben | 10 |
| 5 | Propyl Paraben | 10 |
| 6 | Methanol | 10 |
| 7 | Paraffin | 10 |
| 8 | Glycerin | 10 |
| 9 | Propylene Glycol | 10 |

3. Preparation of Topical Composition

1.0-3.0 gms of Lidocaine HCl dissolved in water and slurry of the 1.0-3.0 gms of the Sildenafil Citrate mixed with the 10:90 or 90:10 w/w of the above emulsified homogenized product of 'A' and 'B' to obtain the final product in the form of ointment. Surfactants, alcohols, humectants, mixture of hydrocarbons, preservatives, chelating agents, water.

## CLAIMS

1. A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) comprising pharmaceutically effective amount of l-[[3-(6,7-dihydro-l-methyl-7-oxo-3-propyl-lH-pyrazolo[4,3-^pyrimidin-5-yl)-4 ethoxyphenyl] sulfonyl] -4-methyl piperazine citrate and desensitizing agent along with pharmaceutically acceptable excipients.

2. A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein desensitizing agent is lignocaine HCL or lidocain.

3. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein l-[[3-(6,7-dihydro-l-methyl-7- oxo-3-propyl-lH-pyrazolo[4,3-^pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl piperazine citrate and desensitizing agent pharmaceutical effective amount is 1-3 w/w.

4. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein pH is 4.0-6.0

5. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1, wherein pharmaceutically acceptable excipients are surfactants, alcohols, humectants, mixture of hydrocarbons, preservatives, chelating agents, water, perfumes.

6. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1, wherein surfactant is Cetomacogol 1000.

7. A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein humectant is glycerin.

8. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein alcohols are Cetostearyl alcohol, cetearyl alcohol or cetylstearyl alcohol, propylene glycol, methanol, ethanol, propanol.

9. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein hydrocarbons are semi solid paraffin, petroleum jelly, soft paraffin.

10. A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 wherein preservatives are methyl paraben, Propyl paraben, methyl ester p-hydroxy benzoic acid.

11. A topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 chelating agent is sodium salt of ethyl diamine tetra acetate EDTA.

12. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 1 the perfumes are natural or synthetic.

13. A method for manufacturing topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) comprising emulsification of aqueous solution of chelating agent containing desensitizing agent and oily base containing pharmaceutically acceptable excipients and homogenizing the mixture at increased temperature under vacuum pressure and adding slurry of l-[[3-(6,7-dihydro-l-methyl-7-oxo-3-propyl-lH-pyrazolo[4,3-^pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methyl piperazine citrate with constant stirring.

14. A method for manufacturing topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 13 wherein temperature is 60 to 100$^{O}$C.

15. A method for manufacturing topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) according to claim 13 wherein in desensitizing agent is lidocaine or lidocain.

16. A method for manufacturing topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) as claimed in claim 13 wherein pharmaceutically acceptable excipients are surfactants, alcohols, humectants, mixture of hydrocarbons, preservatives, chelating agents, water, perfumes.

17. A method for manufacturing topical composition for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH) according to example and description herein.

18. A topical composition for treatment erectile dysfunction and pulmonary arterial hypertension (PAH) according to example and description herein.