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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2011 (23.06.2011)

PCT

(10) International Publication Number
WO 2011/074015 A2

(51) International Patent Classification:
A61K 9/12 (2006.01)

(21) International Application Number:
PCT/IN2010/000824

(22) International Filing Date:
16 December 2010 (16.12.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2920/MUM/2009 17 December 2009 (17.12.2009) IN

(71) Applicant *(for all designated States except US)*: **THEMIS MEDICARE LIMITED** [IN/NA]; 11/12 Udhyog Nagar, S.V. Road, Goregaon (West), Mumbai 400 104 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PATEL, Dinesh, Shantilal** [IN/IN]; 11/12 Udhyog Nagar, S.V. Road, Goregaon (West), Mumbai 400 104, Maharashtra (IN). **PATEL, Sachin, Dinesh** [IN/IN]; 11/12 Udhyog Nagar, S.V. Road, Goregaon (West), Mumbai 400 104, Maharashtra (IN). **KURANI, Shashikant, Prabhudas** [IN/IN]; 11/12 Udhyog Nagar, S.V. Road, Goregaon (West), Mumbai 400 104, Maharashtra (IN).

(74) Agent: **KIRANKUMARI, R., Singh**; Gopakumar Nair Associates, 3rd Floor, "Shivmangal", Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai 400 101 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, TH, 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, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, 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, RS, 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:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

(54) **Title**: NOVEL COMPOSITION OF PHARMACEUTICAL PRODUCT TO TREAT SEXUAL DYSFUNCTION

(57) **Abstract**: Disclosed herein is topical pharmaceutical composition comprising Lidocaine or it pharmaceutically acceptable salts in combination with one or more other local anesthetic agent(s) along with propellants, solvents and other pharmaceutically acceptable excipient useful for the treatment of premature ejaculation and like conditions optionally with additional therapeutic active ingredient(s).

WO 2011/074015 A2

"NOVEL COMPOSITION OF PHARMACEUTICAL PRODUCT TO TREAT SEXUAL DYSFUNCTION"

Technical Field of the Invention:

The present invention relates to an aerosol formulation containing Lidocaine in combination with another local anesthetic agent preferably, Prilocaine and/or other active ingredient(s) for topical application, which can be applied to glans penis to achieve local anesthesia of the dorsal neurons of the penis for the treatment of premature ejaculation. More particularly, the invention relates to Lidocaine and Prilocaine in optimum ratio in the form of pump spray, when applied locally to the glans penis which provides delayed time of sexual intercourse to make the men and women sexually satisfied. The formulation also helps to alleviate other physiological conditions affecting the mammals related to intercourse.

Background of the Invention:

It is known that Lidocaine and Prilocaine are among the first amino amide-type local anesthetics. Chemically, Lidocaine is 2-(diethylamino) - *N*-(2, 6-dimethylphenyl) acetamide and Prilocaine is (*RS*)-*N*-(2-methylphenyl)-N^2-propylalaninamide.

Lidocaine and Prilocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action. These are thought to act within sodium channels of the nerve membrane.

As has been previously established, a normal sexual response cycle comprises four interactive, nonlinear stages: desire, arousal, orgasm and resolution. In males, orgasm usually coincides with ejaculation, but represents a distinct cognitive and emotional cortical event. Ejaculatory dysfunction is one of the most common male sexual disorders. Ejaculatory dysfunction can cause considerable distress to men of all ages about their sexual function. In a recent survey of 12815 men aged 50–80 years, 46% had an ejaculatory disturbance and 59% were 'highly bothered' by it, particularly if they also had lower urinary tract symptoms. (Reference: David J. Ralph, Kevan R. Wylie., Ejaculatory disorders and sexual function. BJU Int., 2005; 95; 1181 – 1186). The most common ejaculatory dysfunction is premature ejaculation (PE). Premature ejaculation is the

inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse. PE affects 5–40% of sexually active men. (Reference: Carlo Bettocchi, Paolo Verze, Fabrizio Palumbo, Davide Arcaniolo and Vincenzo Mirone. Ejaculatory disorders: pathophysiology and management, *Nature Clinical Practice Urology* (2008) 5, 93-103). Premature ejaculation (PE) is a common male sexual dysfunction with a approximate prevalence of about 30%. It was estimated that 75% of men may experience PE at some point in their sexual lifetime. The inability to control the timing of ejaculation may cause reduced confidence, increased sexual anxiety and performance anxiety. (Reference: Dr. Siu-king MAK Medical Treatment of Premature Ejaculation Medical Bulletin *VOL.14 NO.10 OCTOBER 2009)*. The condition results in frustration for both sexual partners and can, in extreme cases, result in an inhibition of relationships. The problem of premature ejaculation is not the result of prolonged absence from sexual activity. The inability to delay ejaculation on all or nearly all vaginal penetrations; the prominent reason for such inability may be the negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Sometimes forceful coitus also results in a painful condition to delicate organs and sexual dissatisfaction for both partners. Since heightened sensitivity of the glans is implicated in premature ejaculation, it seems reasonable that reducing this sensitivity could have a delaying effect on intravaginal ejaculation latency time (IVELT) without adversely affecting the sensation of ejaculation.

Ideally, for treatment of premature ejaculation in males, targeted delivery to the penis is required whereby local, regional, effects of the drug are enjoyed but such that systemic distribution and subsequent systemic effects can be avoided.

Local anesthetics are traditionally injected into the desired site with a syringe. Most formulations of local anesthetics are aqueous solutions designed for injection into tissue, around nerves, or into the epidural spaces. Syringe can not be used to administer the lcoal anesthetic on the glans penis before sexual intercourse.

A marketed cream containing a local anesthetic, may be an alternative treatment for PE. However, the active ingredients of such formulation take a long time to penetrate the glans so that the formulations would need to be applied well in advance of sexual activity, which can limit spontaneity. Further, the cream is greasy, difficult to administer, and requires the use of a condom in order to prevent partner transfer. Finally, as such marketed formulation penetrates keratinized skin, it numbs the whole of the penis, not just the glans, which can compromise sexual satisfaction.

Hence, there exist a need to develop the aerosol spray formulation containing Lidocaine and Prilocaine for direct local application to glans penis and thereby achieving delayed ejaculation for maximum possible sexual pleasure. Further, such formulation can also alleviate microinjuries at the site if the same is formulated and combined with other agents.

US20070269465 discloses a mixture of Lidocaine, Prilocaine and tetracaine, or their pharmaceutically acceptable salts to be filled in tubes and the same has been studies for itching, erythema, cuteneous rash and edema in the patients. This invention does not mention the use of the formulation for premature ejaculation.

US5446070 relates to bioadhesive formulation for topical application containing local anesthetic agents to prevent or ameliorate pain. This invention does not give any information about the use of the formulation for premature ejaculation. Moreover, it is in bioadhesive device form so can not be applied to glans penis during intercourse.

US5698227 provides compositions comprising Lidocaine and oil for topical administrations for their use in various surgeries and interventions without the need for subcutaneous injections of local anesthetics. The cited prior art further provides a compartmentalized kit having a first container providing oil and a second container providing an aqueous solution of Lidocaine. This invention too is not meant for premature ejaculation.

US6299902 discloses a formulation containing at least one local anesthetic agent and melting point depressing agents like thymol and ethanol to provide anesthesia formluated in the form of creams. This invention is only meant for creams and doesn't involve

preparation of spray systems of local anesthetic and also doesn't implicate the use of such formulation in treating preamature ejaculation.

US5679325 combines the local anaesthetic Lidocaine in free base form and the non-CFC aerosol propellants for providing formulation to the patient's respiratory system directly or by way of an airway. Here also use of such formulation for the treatment of premature ejaculation has not been reported.

US5827529 discloses an external preparation for application to the skin containing Lidocaine which comprises a drug-retaining layer placed on a support, wherein said drug-retaining layer comprises an adhesive gel base and Lidocaine, said base comprising a water-soluble high molecular weight substance, water and a water-retaining agent, which can release the active Lidocaine gradually and constantly so that Lidocaine is transdermally absorbed for a long period of time. This invention doesn't mention use of Lidocaine for the treatment of premature ejaculation.

US5453445 relates to an aerosol-dispensable pharmaceutical composition consisting essentially of a combination of Lidocaine free base, a pharmacologically-acceptable phenylephrine acid addition salt, and a pharmacologically-acceptable organic solvent. This prior art provides the use of vasoconstriction but does not hint about treatment of premature ejaculation.

US20090093547 discloses a propellant free formulation for treating premature ejaculation comprising combination of Prilocaine and Lidocaine.

US5858331 provides novel aerosol formulations which include Prilocaine, with or without additional medicaments, in HFC propellants, without additional organic solvents and surfactants. Prilocaine base, in liquid and micro rod crystal form, can be solubilized within hydrofluorocarbon propellants to produce a stable, oily liquid. It does not report the use of lidocain for the treament of premature ejaculation.

US4529601 discloses a locally active anesthetic agent in the form of homogenous oil which is useful for topical or parenteral application, consisting essentially of Prilocaine in

the form of its base in admixture with Lidocaine, in the form of its base. This invention mentions the indication for antiperspirant compositions.

US2002006435 discloses a local, topical transdermal anesthetic and vasodilator formulation comprising e topical anesthetic and vasodilator and pharmaceutically acceptable carrier wherein topical anesthetic agent comprises a eutectic mixture of Lidocaine and Prilocaine. The formulation is in the form of spray but does not hint for the excipients which have enhanced penetrating effect and rapid onset of action.

US6031007 relates to combination of Lidocaine and Prilocaine in the gel form.

US20070207193 discloses a method of ameliorating neurogenic tremor in mammals which comprises topical anesthetic composition comprising Lidocaine and Prilocaine in a form of spray solution but does not hint about premature ejaculation.

EP20010121321 discloses use of a mixture from Lidocaine and Prilocaine to prepare pharmaceutical formulation for local application but not for premature ejaculation.

WO/2009/026414 relates to topical anesthetic composition comprising Lidocaine and Prilocaine in spray form for Modulation of Neurogenic Tremor.

WO/1993/017674 relates to topical use of local anesthetic agents for rheumatoid arthritis. The Local anesthetic is a eutectic mixture of Lidocaine and Prilocaine.

WO/1989/011853 discloses the use of local anesthetic agents in the manufacture of preparations with wound healing effect. The Local anesthetic is an eutectic mixture of Lidocaine and Prilocaine but doesn't cover indication for the treatment of premature ejaculation.

Various inventions mentioned in the prior arts relate to compositions containing Lidocaine for providing local anesthetic effect but none have developed formulation especially for the particular indication in the treatment of premature ejaculation which contains Lidocaine in combination with Prilocaine in optimum ratio incorporated in

aerosol pump spray system using suitable propellants and solubilisers which are harmless for application on the glans penis and no patent depicts the claim of clinical usefulness of compounds.

Treatment of premature ejaculation can be improved by inventing alternative to overcome the problems associated with traditional approaches. Hence, inventors were motivated to develop the locally acting composition for the effective treatment of premature ejaculation and for proving its usefulness.

Summary of the Invention:

The present invention is directed towards the pharmaceutical composition for the treatment of premature ejaculation and other physiological conditions affecting the mammals. The present invention is meant for topical application in the form metered dose aerosol spray which contains Lidocaine either as a free base or as pharmaceutically acceptable salts thereof in combination with one or more local anesthetic agents preferably, Prilocaine or its salts thereof which are incorporated into suitable propellants, solvents and other pharmaceutically acceptable excipients. Such formulated composition when sprayed on to glans penis, it delivers predetermined and therapeutically effective amount of active substances to achieve local anesthesia of the dorsal neurons of the penis.

The compositions may further contain one or more additional pharmaceutically active agents. The compositions may be formulated as a pump spray with or without propellant, creams, gels, ointments, solutions, foam, balm, suspensions, emulsion, lotion, pastes, to achive local anesthesia of the glans penis for premature ejaculation and for treating other physiological conditions affecting the mammals.

In another aspect, the invention provides a local composition(s) containing an effective amount of one or more local anesthetics to cause desensitization of the neurons of the glans penis and methods of making and using thereof.

Detailed Description Of The Invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The present invention describes a metered dose aerosol composition comprising Lidocaine or its salts thereof in combination with one or more local anesthetic agent(s) or their salts thereof for local application to glans penis for providing local anesthesia to dorsal neurons of the penis for the treatment of premature ejaculation. The present composition when sprayed to the glans penis it delivers predetermined amount of active substances for achieving local anesthesia and thereby provides delayed sexual intercourse for maximum sexual pleasure for both the partners. It further also helps to treat other conditions encountered during the sexual intercourse.

More specifically, the present invention describes a topical metered dose aerosol composition comprising Lidocaine either as a free base or as pharmaceutically acceptable salts thereof in combination with one or more local anesthetic agents preferably, Prilocaine or salts thereof in therapeutically effective amount alone or in combination with other anesthetic drug(s) or other drugs which are incorporated with suitable propellants, solvents and other pharmaceutically acceptable excipients. Such formulation can be sprayed on to keratinized tissue to achieve therapeutic effect. Such composition when sprayed on to glans penis, it delivers predetermined and therapeutically effective amount of active substances for desensitization of the site.

In an embodiment, the present invention provides a metered dose spray dispenser for delivery of the active substances of composition of the present invention. Metered-dose spray dispenser consists of three major components; the canister, where the formulation resides; the metering valve, which allows a metered quantity of the formulation to be dispensed with each actuation; and an actuator (or mouthpiece) which allows the patient to operate the device and directs the aerosol onto the patient's application site. The formulation itself is made up of the drug, a liquefied gas propellant and, in many cases, stabilising excipients. The actuator contains the mating discharge nozzle and generally includes a dust cap to prevent contamination. To use the metered dose aerosols the patient

presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are applied to the desired area. (Reference: *Pharmaceutical Inhalation Aerosol Technology*, ed. A. J. Hickey, 2nd edition, Marcel Dekker Inc., NY, 2004. and Swarbrick, James (2007). *Encyclopedia of Pharmaceutical Technology* (3rd Illustrated ed.). Informa Health Care. pp. 1170.) The main advantage of the metered dose spray dispenser system is that it delivers exact predetermined amount of formulation upon each actuation. This is very useful in case of potent drugs where the safety and toxicity are of the prime concerns. Ultimate result is that safe and effective amount of medicament is delivered which is predetermined for providing the desired action.

Thus, in another preferred embodiment, the present invention describes a pharmaceutical composition for topical application comprising: (i) a therapeutically safe and effective amount of Lidocaine or of a pharmaceutically acceptable salt thereof; (ii) a therapeutically safe and effective amount of Prilocaine or its pharmaceutically acceptable salt thereof, and optionally another local anesthetic agent in therapeutically allowed amount.

In a particular embodiment, the composition further comprises Lidocaine or pharmaceutically accpetable salts thereof in combination with Prilocaine or pharmaceutically acceptable salts thereof alone or in combination with other local anesthetic drug(s) formulated into metered dose aerosol container meant for spraying onto by keeping the aerosol container 5 centimeters away from the application site.

In another embodiment, the pharmaceutical composition further comprises of above mentioned active substances with appropriate amounts of pharmaceutically acceptable excipients to constitute a topical formulation. The composition comprises of different types of excipients such as propellants, solvents, solubilisers, skin penetration enhancers, spreading agents, viscosity increasing agents, surfactants, preservatives and emulsifiers. Optionally, other components such as flavors, natural & synthetic oils, fragrances,

essence of fruits can be added to the compositions of present invention in appropriate amounts to enhance the aesthetic appeal of the formulation & makes it more acceptable.

The composition may further optionally comprise of suspending agents, pH modifying agents, antioxidants, chelating agents, diluents, and emmolients in suitable amounts. The pharmaceutically acceptable excipient(s) used in the present invention is in amount of 10 % to 95 % by weight in concentration. The compositions may further contain one or more additional pharmaceutically active agents. The compositions may be formulated as a pump spray with or without propellant, creams, gels, ointments, solutions, foam, balm, suspensions, emulsion, lotion, pastes, to achive local anesthesia of the glans penis.

Further, the present composition comprises of active agents in the form of microparticles, microspheres, liposomes, ethosomes or nanoparticles, which may be formed of active agent alone or in combination with an excipient or carrier.

The concentration of single active drug or total concentration of all the active anesthetic drugs in the formulation can vary up to about 1 % to 10 % by weight, about 15% by weight, about 20 % by weight, about 25% by weight, about 30% by weight, about 35 % by weight, about 35% by weight, about 40 % by weight, about 45 % by weight, about 50% by weight, about 55 % by weight, about 60 % by weight, about 65 % by weight, about 70 % by weight, about 75 % by weight, about 80 % by weight, about 85% by weight, about 90% by weight, and about 95 % by weight.

Lidocaine and Prilocaine or any other local anesthetic agent apart from Prilocaine can be mixed together in various ratios. In preferred embodiment, Lidocaine and Prilocalne are mixed together in the ratio of 75:25. Further, Lidocaine and Prilocaine are mixed together in ratio such as 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, 60:40, 55:45, 50:50, 45:55, 40:60, 35: 65, 30:70, 25:75, 20:80, 15:85, 10:90, and 5:95.

The present invention contains solvent which is also used for the purpose of solubiliser. The preferred solvent used for preparing the drug solution in the present composition is diethylene glycol monoethy ether in an amount of about 20 to 40 % w/w.

The aerosol composition of the present invention is formulated either in monophasic liquid system as a solution or biphasic liquid system. Examples of such biphasic liquid

system include emulsion, suspension, colloidal dispersion, dispersion systems, microemulsions, and multiple phase emulsions. The aerosol is formulated using foam aerosol system. The particles in the dispersed phase may be in the form of micronised form, microparticles, microspheres or nanoparticles either made up of active pharmaceutical ingredient alone or in combination with suitable carriers or excipients.

In another embodiment of the present invention at least one active pharmaceutical ingredient(s) may be selected from the group which consists of tetracaine, bupivacaine, mepivacaine, Articaine, Carticaine, Cinchocaine/Dibucaine, chlorprocaine, dibucaine, etidocaine, hexylcaine, procaine, ketamine, pramoxine, dyclonine and phenol, Levobupivacaine, Piperocaine, Ropivacaine, Trimecaine, Benzocaine, Chloroprocaine, Cocaine, Cyclomethycaine, Dimethocaine/Larocaine, carbisocaine, ciprocaine, butanilicaine and trimecaine, Propoxycaine, Procaine, Proparacaine, Tetracaine/Amethocaine and natural local anesthetics like Saxitoxin and Tetrodotoxina derivative or prodrug thereof, and combinations thereof.

In another embodiment of the present invention describes topical composition comprising Lidocaine and/or Prilocaine or any other suitable local anesthetic agent which can be formulated in combination with other local anesthetic agent such as propofol, fospropofol or centbucridine and its salts thereof for directly application through suitable route for delivery of these anesthetic drugs in mammals.

In another embodiment of the present invention, the topical composition of Lidocaine and/or Prilocaine can also be formulated in combination with other compounds used for treatment of sexual dysfunction which may be selected from the group of but not limited to Phosphodiesterase type 5 (PDE5) inhibitor like sildenafil, Tadalafil, Vardenafil, Acetildenafil, Lodenafil, Mirodenafil, Thiomethisosildenafil, Udenafil, Avanafil Doxazosin, Tamsulosin; serotonin reuptake inhibitor antidepressants like dapoxetine, Clomipramine, Fluoxetine, Paroxetine, sertraline, flibanserine (for women), antidepressant is selected from the group for formulating in combination with lidocaine and prilocaine selected from amesergide, amineptine, amitriptyline, amoxapine, benactyzine, brofaromine, bupropion, butriptyline, cianopramine, citalopram, clomipramine, clorgyline, clovoxamine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, etoperidone, femoxetine, fezolamine, fluoxetine,

fluvoxamine, ifoxetine, imipramine, iprindole, isocarboxazid, levoprotiline, lofepramine, maprotiline, medifoxamine, melitracen, metapramine, methylphenidate, mianserin, milnacipran, minaprine, mirtazapine, moclobemide, nefazodone, nialamide, nomifensine, nortriptyline, opipramol, oxaflozane, oxaprotiline, oxitriptan, paroxetine, phenelzine, pirlindole, propizepine, protriptyline, quinupramine, rolipram, rubidium, and combinations thereof.

In another embodiment of the present invention, Lidocaine and/or Prilocaine or any other suitable local anesthetic agent can also be formulated in combination with herbal extracts of certain plants which are remedies for the treatment of premature ejaculation and the like. Examples of such plants extracts include but are not limited to the extracts of *Mucuna pruriens, Ginseng redix alba, Angelicae gigantic radix, Cistanchis herba, Zanthoxylli fructs, Torlidis semen, Asiasari radix, Caryophylli flos, Cinnamoni cortex,* and *Bufonis veneum, Abrus precatorius*. Linn, alone or in combinations of the any of the foregoing.

The premature ejaculation is a disorder which may be due to mixed physical or mental condition of body in which the person ejaculates early & fails to ejaculate at proper or at excited state. Other than mental conditions the physiological condition which can lead to premature ejaculation are Arteriosclerosis, Benign prostatic hyperplasia, Cardiovascular disease, Diabetes, Injury to the sympathetic nervous system, Pelvic injuries, Prostate cancer, Prostatitis, Urethritis, Urinary incontinence, Polycythemia, Polyneuritis, painful coitus. The present formulation can be given in the combination with suitable therapeutic agents which are used for the treatment or management of above mentioned medical conditions that contribute to premature ejaculation.

Lidocaine in combination of one or more local anesthetic agent can also be sprayed onto innner side wall of condoms after dissolving in suitable vehicle or solvent or lubricating fluid for achieving delayed time for ejaculation.

The topical composition comprising Lidocaine and/or Prilocaine can also be combined with haemostatic agents such as feracrylum which is known for its property to stop micro capillary which also has antimicrobial activity. These can be formulated according to present inventions for its use in painful coitus and for treating painful wound conditions.

Such formulation can be very useful for treating the painful coitus as there are chances of micro-bleeding from the sex organs during intercourse as the haemostatic agents along with local anesthetic agents are present in the composition which will help to stop bleeding and at the same time will provide anesthetic action.

The present topical composition comprising one or more local anesthetic agents mentioned above in the present formulation can be formulated in combination with suitable painkillers & therapeutic drugs. Painkiller drugs can be selected from the therapeutic categories like analgesic, antipyretic, Non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs in therapeutically allowed doses. Non limiting examples of such categories of non-steroidal drugs include analgesics, antipyretics include from class aniline and p-Aminophenol analogues, salicylic acid analogues, quinoline derivatives, pyrazolones and pyrazolidones, N- arylanthranilic acid, drugs from the category NSAID's includes heteroarylacetic acid analogues, arylacetic acid analogues, arylpropionic acid analogues, naphthalene acetic acid analogues, gold compounds, uricosuric agents, salicylic acid analogues, pyrazolones and pyrazolidones, lipo-oxygenase-2 inhibitors like licofelone, COX-2 inhibitors like celecoxib, etoricoxib, lumiracoxib and other classes of drugs. Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the dermatologically acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for local application. Examples of steroidal drugs include but are not limited to corticosteroids such as hydrocortisone and hydrocortisone butyrate, hydroxyl-triamcinolone, alpha-methyl dexamethasone, amcinafel, amcinafide, beclomethasone dipropionates, betamethasone and of its esters, chloroprednisone, chlorprednisone acetate, clescinolone, clobetasol valerate, clocortelone, cortisone, cortodoxone, dexamethasone-phosphate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, methylprednisolone, triamcinolone acetonide, flucetonide, fludrocortisone, fluradrenolone, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, diflurprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone

cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof and combinations of any of the foregoing.

Lidocaine and Prilocaine or other local anesthetic agents can be combined with anti-histaminic drugs to formulate the pump spray aerosol formulation of the present invention for local/topical application for the treatment of topical allergic conditions. Antihistaminic drugs which may be included are but not limited to H1 receptor antagonists like rupatadine, diphenhydramine, loratadine, desloratadine, meclizine, quetiapine, fexofenadine, pheniramine, cetirizine, promethazine, chlorpheniramine, and levocetirizine; H2 recepor antagonist like cimetidine, famotidine, ranitidine, nizatidine, roxatidine, and lafutidine; H3 recptor antagonists like ciproxifan, clobenpropit and thioperamide; H4 receptor antagonists like thioperamide.

In another embodiment of the present invention, the topical composition comprising Lidocaine and Prilocaine or any other suitable local anesthetic agent can also be formulated in combination with vasodilators compounds which may be selected from the group of but not limited to, Alpha-adrenoceptor antagonists (alpha-blockers), Angiotensin converting enzyme (ACE) inhibitors, Angiotensin receptor blockers (ARBs), Beta$_2$-adrenoceptor agonists (β_2-agonists), Calcium-channel blockers (CCBs), Centrally acting sympatholytics, Direct acting vasodilators , Endothelin receptor antagonists , Ganglionic blockers , Nitrodilators, Phosphodiesterase inhibitors, Potassium-channel openers, and Renin inhibitors.

In another embodiment, the present invention describes, the topical composition comprising Lidocaine and Prilocaine or any other suitable local anesthetic agent which can be formulated in combination with antimicrobial agent(s). Examples of such antimicrobial agents which may be formulated in the present invention include but are not limited to antibacterial, antifungal, antiprotozoal and antiviral agents, such as beta-lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, a tetracycline, tetracycline derivatives, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, such as chlortetracycline, methacycline and its salts, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, streptomycin, tobramycin, and

miconazole. Also included are tetracycline hydrochloride, famesol, erythromycin estolate, erythromycin stearate (salt), amikacin sulfate, doxycycline hydrochloride, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, Tioconazole, miconazole and salts thereof, nadifloxacin, mometasone furoate, Terbinafine and its salts thereof, amanfadine hydrochloride, amanfadine sulfate, triclosan, octopirox, nystatin, tolnaftate, clotrimazole, anidulafungin, micafungin, voriconazole, lanoconazole, ciclopirox, econazole, further aloprostil and mixtures thereof.

In another embodiment, the present invention describes a topical composition comprising Lidocaine and Prilocaine or any other suitable local anesthetic agent, can also be formulated in combination with an N-methyl d-aspartate (NMDA) receptor antagonist which involves in anti-excitotoxic activity in humans, a μ-opiate analgesic such as tramadol, and optionally a cytochrome P450 inhibitor such as quinidine, is very effective in delaying the onset of ejaculation in male humans who have erection as well as ejaculation problem.

Further the present invention may also be formulated in combination with NMDA receptor antagonist like dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

In another embodiment, the present invention describes a topical composition comprising Lidocaine and Prilocaine or any other suitable local anesthetic agent which can be further formulated in combination with cytochrome P450 inhibitor that is quinidine, quinine, naphthyridine, xanthine, phenoxy amino alkane, carbamoyl imidazole, a guanidine imidazole, cimetidine, quinoline, chloroquine, primaquine, fluvoxamine, or pharmaceutically acceptable salts thereof.

The serotonin agonist may also be used in combination with the present invention which is selected from the group consisting of 2-methyl serotonin, buspirone, ipsaperone, tiaspirone, gepirone, lysergic acid diethylamide, ergot alkaloids, 8-hydroxy-(2-N,N-dipropylamino)-tetraline, 1-(4bromo-2,5-dimethoxyphenyl)-2-aminopropane, cisapride, sumatriptan, m-chlorophenylpiperazine, trazodone, zacopride, mezacopride and combinations thereof. The suitable serotonin antagonist is selected from the group consisting of ondansetron, granisetron, metoclopramide, tropisetron, dolasetron, trimethobenzamide, methysergide, risperidone, ketanserin, ritanserin, clozapine, amitryptiline, azatadine, cyproheptadine, fenclonine, dexfenfluramine, fenfluramine, chlorpromazine, mianserin, and apomorphin that is a non-selective dopa receptor agonist and combinations thereof.

For many forms of erectile dysfunction, treatment may be undertaken with drugs sprayed directly on to the penis, including drugs such as papaverin, prostaglandin E_1, phenoxybenzamine or phentolamine along with the local anaesthetic like lidocaine prilocaine, benzocaine, bupivacaine alone or/and combination thereof and applied with penetration enhancer.

The adrenergic antagonist which may be combined with present formulation which are selected from the group consisting of phenoxybenzamine, phentolamine, tolazoline, prazosin, terazosin, doxazosin, trimazosin, yohimbine, ergot alkaloids, labetalol, ketanserin, urapidil, alfuzosin, bunazosin, tamsulosin, chlorpromazine, haloperidol, phenothiazines, butyrophenones, propranolol, nadolol, timolol, pindolol, metoprolol, atenolol, esmolol, acebutolol, bopindolol, carteolol, oxprenolol, penbutolol, carvedilol, medroxalol, naftopidil, bucindolol, levobunolol, metipranolol, bisoprolol, nebivolol, betaxolol, carteolol, celiprolol, sotalol, propafenone, indoramin, and combinations thereof. Further, adrenergic neurone blocker may also be combined and selected from the group consisting of bethanidine, debrisoquine, guabenxan, guanadrel, guanazodine, guanethidine, guanoclor, guanoxan, and combinations thereof.

The formulation may also contain cooling agents like thymol or menthol to provide cooling sensation on the applied area.

Present embodiment may also contain substances like thymol and ethanol for bringing down the melting point of Lidocaine, Prilocaine and other suitable local anesthetic agents.

Propellants are the most important part of the aerosol system. Propellants used in embodiment of the present invention are 1,1,1,2 Tetrafluoroethane which is also known as R-134a, Genetron 134a, Suva 134a or HFC-134a. It is a propellant with thermodynamic properties similar to R-12 CH_2FCF_3, and a boiling point of −26.3 °C (−15.34 °F). The preferred concentration of the propellant in the present composition is in the range of 40% w/w to 70 % w/w. The advantage of this propellant is that it is non-flammable vapor at room temperature and atmospheric pressure. It neither contains chlorine atoms and, as such, neither are implicated in stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons.

Other propellants which may be selected in the embodiment of the present invention may include but not limited to the chemically-inert hydrocarbons such as dimethyl ether, compressed air, propane, n-butane, isobutane and cyclopropane, and mixtures thereof, as well as halogenaed hydrocarbons such as dichlorodiluoromethane; 1,1-dichloro-1,1,2,2-tetrafluoroethane (propellant 114); 1-chloro-1,1-difluoro-2,2-trifluoroethane (propellant 115); 1-chloro-1,1-difluoroethylene (propellant 142B);1,1-difluoroethane (propellant 152A); 1,1,1,2,3,3,3- hepta fluoropropane, dimethyl ether and monochlorodifluoromethane, and mixtures thereof.

Present invention comprises of solubilizer selected from glycol ethers such as ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monopropyl ether, ethylene glycol monoisopropyl ether, ethylene glycol monobutyl ether, ethylene glycol monophenyl ether, ethylene glycol monobenzyl ether, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether and diethylene glycol mono-n-butyl ether preferably diethylene glycol monoethyl ether commercially known as Transcutol-P. Glycol ethers are a group of solvents based on alkyl ethers of ethylene glycol. These solvents typically have higher boiling point, together with the favorable solvent properties of lower molecular weight ethers and alcohols. Glycol ethers can be derived of diethylene glycol (carbitols Transcutol-P is a powerful solubilizer and good penetration enhancer.

Further, solvents like glycerol esters of fatty acids, medium chain triglycerides may be used as a vehicle for dissolving the drug. Further, solvents which may be used as lubricants include but are not limited to glyceryl behenate, behenoyl macrogolglycerides, glyceryl palmitostearate and glyceryl palmitostearate.

Other solubilisers as well as emulsifiers which may be included are but not limited to fluorinated alkyl esters; polyethoxylated sorbitan ester, such as polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monopalmitate, polyethoxylated sorbitan monostearate, polyethoxylated sorbitan tristearate, and polyethoxylated sorbitan monooleate; trioleate polysorbates; and any combination of any of the foregoing.

Emulsifiers are selected from the group of metallic soaps, certain animal and vegetable oils, and various polar compounds. Other excipients which are suitable as emulsifiers includes xanthan gum, tragacanth, propylene glycol and its alginate forms, steartes, sunflower oil, triethonolamine, acacia, anionic emulsifying wax, sodium citrate , calcium stearate, carbomers, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, ethylene glycol palmitostearate, glycerin monostearate, glyceryl monooleate, cellulose derivatives like methyl cellulose, hydroxy propyl cellulose, hydroxy propyl methylcellulose, lanolin and its alcohol forms, various mineral oils, medium-chain triglycerides, monobasic sodium phosphate, monoethanolamine, nonionic emulsifying wax, oleic acid, poloxamer, poloxamers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, propylene glycol alginate, self-emulsifying glyceryl monostearate, and combinations of any of the foregoing.

Vehicles or diluents or bulking agents may optionally be included in the composition to incorporate, disperse or dissolve the active ingredient. Examples of suitable diluents include, but not limited to, purified water, alcohols, low molecular weight glycols, low molecular weight poyols, organic hydrophilic solvents and and combinations of any of the foregoing.

pH Modifiers or pH adjustment agents may optionally be included in the present invention selected from group of but not limited to hydrochloric acid, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, citric acid, tartaric acid, acetic acid, potassium citrate, sodium citrate, phosphoric acid, succinic acid, lactic acid,

ammonium hydroxide, magnesium oxide, calcium carbonate, magnesium carbonate, magnesium aluminum silicates, malic acid, sodium phosphate, gluconic acid, tetracarboxylic acid, fumaric acid, diethanolamine, monoethanolamine, triethanolamine, and combinations thereof.

The present composition may optionally include moistening agents or humectants selected from, but are not limited to triacetin, propylene glycols, glycerin, butylene glycol, propylene glycol, sorbitol, and combinations thereof.

Surfactant can serve the purpose of solibiliser, wetting agents, emmollients, anti-foaming agents, detergents, anticaking agents, viscosity enhancers, emulsifier and suspending agents. Surfactants may be selected from the class of Non-ionic surfactants, amphoteric or zwitter ionic surfactants, anionic surfactants and cationic surfactants. Examples of such Ionic surfactants which may be included in the present invention include but not limited to Anionic surfactants like sulfonated alpha olefins, alkylbenzenesulfonic acid and its derivatives (based on sulfate, sulfonate or carboxylate anions) perfluorooctanoate (PFOA or PFO), perfluorooctanesulfonate (PFOS), sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, and other alkyl sulfate salts , sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES), alkyl benzene sulfonate , soaps, or fatty acid salts; cationic surfectants like cetyl trimethylammonium bromide, hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts, cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), Benzalkonium chloride (BAC), benzethonium chloride (BZT); zwitterionic (amphoteric) surfectants like dodecyl betaine, cocamidopropyl betaine, coco ampho glycinate. Nonionic surfectants which may be used include but not limited to ethoxylates, nonylphenol alkoxylates, ethoxylates and alkoxylates of fatty alcohols, alkyl polyethylene oxides, alkylphenol polyethylene oxides, copolymers of polyethylene oxides and polypropylene oxide commercially called poloxamers or poloxamines. Surfactants from the class of alkyl polyglucosides may be selected which may include but not limited to octyl glucoside and decyl maltoside. Surfactants from fatty alcohols class may include but not limiting to cetyl alcohol and oleyl alcohol. Further surfactants including polyoxyethylene glycols, ethanoloamines, cocamide MEA, and cocamide DEA, dodecyl dimethylamine oxide and polysorbates such as Tween 20, Tween 80 may be included.

The invention may contain other type of surfactants, such as polyoxyethylene alkyl ether, polyoxyethylene alkyl phenyl ether, polyoxyethylene styrenated phenol, the fatty ester of polyoxyethylene hardening castor oil, diglyceryl alkyl ester and the like. Surfectant from the group of sorbitan fatty esters is exemplified by but not limited to sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, sorbitan monostearate and the like. On the other hand, the polyoxyethylene polyoxypropylene alkyl ethers are exemplified by but not limited to polyoxyethylene polyoxypropylene cetyl ether, polyoxyethylene polyoxypropylene lauryl ether, polyoxyethylene polyoxypropylene stearyl ether, polyoxyethylene polyoxypropylene decyltetradecyl ether, and the like.

Penetration enhancers may be included in the composition for enhancing absorption of active drug substance at the local site. Penetration enhancers may act by one or more of mechanisms like disruption, hydration of the stratum corneum lipid layer, interacting with intercellular protein, improved partition of the drug. The penetration can also be enhanced by incorporating co-enhancer or solvent into the stratum corneum. In the present formulation diethyleneglycol monoethyl ether (Transcutol-P) is included which serves both functions of solubiliser as well as penetration enhancer. Other penetration enhancers like glycols, fatty acids and non-ionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) may be used as for penetration enhancement purpose. Examples of suitable penetration enhancers may include but are not limited to terpenes, terpenoids, azones, essential oils like eucalyptol (1,8-cineole), d-limonene and oleic acid, extracts of amomum cardamomum, extracts of elettaria cardamomum, unsaturated sesquiterpene, pyrrolidones and their derivatives, oleic acid, capric acid, lauric acid, neodecanoic acid, palmitoleic acid, fatty acid extract of cod liver oil, salicylic acid, sulfoxides & similar compounds, dimethylacetamide (DMA), N,N-diethyl-m toluamide (DEET), decylmethyl sulfoxide (DCMS) *N,N*-Dimethyloctanamide, *N,N*-dimethyldecanamide, cyclic urea, phospholipids & derivatives, cyclodextrins, papain, amino acid derivatives, dodecyl *N,N*-dimethylamino isopropionate and combinations of any of the foregoing.

Soothing agents may be included in the composition for their emmolient effect. Examples of soothing agents include but are not limited to ethylhexylstearate , ethylhexyl palmitate, glycerin monostearate, glyceryl monooleate, almond oil, castor oil, mineral oils, alkyl palmitates, ceratonia extract, petrolatum base, cetostearoyl alcohol, cetyl

alcohol, lanolins and their alcohols, xylitol, various vegetable oils, cetyl esters wax, cholesterol, cyclomethicone, glycerol stearates, ethylene glycol palmitostearate, glycerin, lecithin, light mineral oil, medium-chain triglycerides and any combination of any of the foregoing.

Suitable antioxidants may be included in the composition to maintain the stability of the formulation. Examples of such antioxidants include but are not limited butylated hydroxyanisole, butylated hydroxytoluene, butyl gallate, propyl gallate, tocopherols, Vitamin C and its derivatives, fumates, malic acid, propyl gallate, uric acid, folic acid, flavons or flavonoids, various aminoacids, carotenes and their derivatives, pharmaceutically acceptable salts thereof, derivatives thereof, and combinations of any of the foregoing.

Preservatives may be included in the composition. Examples of suitable preservatives include but are not limited to parabens, sodium benzoate, benzoaic acid, benzalkonium chloride, thiomersol, benzethonium chloride, chlorobutanol, cetypyridinium chloride, phenol and others and combinations of any of the foregoing.

Present invention may also contain suitable chelating agents. Non limiting examples of such chelating agents include, sodium salts of phosphonic acids, such as bis(hexamethylene)triamino penta(methylene phosphonic) acid and phosphoric acid; sodium salts of citric acid; sodium salts of ethylenediaminetetraacetic acid (EDTA), disodium edetate; and any combination of any of the foregoing.

The composition may include suitable evaporation retardants in the aerosol system. Examples of such evaporation retardants include, but are not limited to, silicone fluid, a water-based wax emulsion, paraffin oil, paraffin wax, and any combination of any of the foregoing.

Present composition optionally includes suitable coupling agent(s) selected from but not limited alkylene glycols, dimethylsulfoxide and any combination of any of the foregoing.

The composition optionally comprise spreading agent, which facilitates uniform spread of anesthetic agents. Spreading agent may be selected from hyalurodinases and/or derivatives of mucopolysaccharidases.

The present invention optionally comprises rheology modifiers. Such viscocity imparting agents or rheology modifiers include but are not limited to, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, xanthan gum, fumed silica, precipitated silica, castor oil, and any combination of any of the foregoing preferably cellulose derivatives.

Corrosion inhibitors may be included in to the composition to control the corrosive action of the formulation on an aerosol spray can as well as on metal substance of the canister of aerosol composition. Suitable corrosion inhibitors include, but are not limited, 2-mercaptobenzothiazole, toluoltriazole, benzotriazole, 2(3H)-benzothiazolethione, morpholine, sodium nitrite, sodium benzoate, and any combination of any of the foregoing.

In a further embodiment, the present invention provides a method of treating symptoms associated with pre-mature ejaculation, which method comprises administering 'an effective amount' of the 'topical composition of present invention' to the subject suffering from pre-mature ejaculation. The subject mentioned herein is mammals or human.

The invention further discloses use of the 'composition of the present invention' in preparing the medicament intended to treat symptoms associated with pre-mature ejaculation.

The present invention can be described by the suitable example but not limiting to the example given below.

Examples:

Example 1:

First solvent diethylene glycol monoethyl ether (29.41% w/w) was taken in suitable container. The Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) were mixed slowly together in solvent with continuous stirring for about 15 min. This was followed by filtration of the so prepared solution. The solution was then filled in to the proper dry lacquered aluminum canisters of specific size. Dip tube and metered valve are placed at

the right place inside the canister. The filled canisters were crimped. Further, the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 58.83% w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 2:

First solvent propylene glycol (5% w/w) was taken in suitable container. The Lidocaine (8.82 % of w/w) & Prilocaine (2.94% w/w) were mixed slowly together in solvent. Isopropyl alcohol (39 % w/w) with continuous stirring for about 15 min. Then menthol (4.24 % w/w) was added to the solution and stirred for 15 minutes to dissolve. The solution was then filled in aluminum canisters. Dip tube is placed at the right place inside the canister. The filled canisters were crimped. Further, the propellant LPG in appropriate quantity (about 40 % w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation. The formulation may be applied without using the metered dose valve.

Example 3:

The spray formulation with Absolute alcohol (27.5 % w/w) formulated by dissolving Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) with continuous stirring for about 15 min. Then the testosterone (12.5% w/w) was added and dissolved. Then menthol (5 % w/w) was added to the solution and stirred for 15 minutes to dissolve. The solution was then filled in to the aluminum canisters. Dip tube and metered valve are placed inside the canister. The filled canisters were crimped. Further the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 43.24 % w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 4:

The solvent diethylene glycol monoethyl ether (29.41% w/w) i.e. transcutol P and drug Vardenafil (10% w/w) along with Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w)

were mixed slowly together in solvent with continuous stirring for about 15 min. The further process was followed as per example 1. The propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 48.83% w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 5:

The formulation of example 4 is formulated by replacing Vardenafil with Sertratiline (50 mg)

Example 6:

The inventive composition of present invention was also successfully developed along with Centbucridine Hydrochloride. The solvent diethylene glycol monoethyl ether (29.41% w/w) and Centbucridine Hydrochloride (1% w/w) along with Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) were mixed slowly together in solvent with continuous stirring for about 15 min. The further process was followed as per example 1. The propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 57.83% w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 7:

The topical spray for treating premature ejaculation was also formulated along with Benzocaine. The spray formulation formulated with absolute alcohol (27.5 % w/w) by dissolving Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) with continuous stirring for about 15 min. Then the Benzocaine (5 % w/w) was added and dissolved. Then menthol (5 % w/w) was added to the solution and stirred for 15 minutes to dissolve. The solution was then filled in to the aluminum canisters. Dip tube and metered valve are placed inside the canister. The filled canisters were crimped. Further the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 50.74 % w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister

was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 8:

The aerosol formulation was also formulated using Yohimbine in its effective concentration of 10% w/w, which is used for erectile dysfunction. The spray system was formulated similarly as per example 1. Yohimbine in its effective concentration was added at the step of dissolving Lidocaine and Prilocaine.

Example 9:

Successful formulation was prepared with Apomorphine which is known for treatment of premature ejaculation and erectile dysfunction. The spray formulation was formulated using absolute alcohol (35 % w/w) in which Lidocaine (8.82 % of w/w), Prilocaine (2.94 % w/w) and Apomorphine (2 % w/w) were dissolved with continuous stirring. The final solution was then filled in the aluminum canisters or suitable container. The filled containers were sealed or crimped. Further the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 51.24 % w/w) was charged with pressure in to the container. Actuator was placed on the container and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 10:

The spray dosage form was also formulated using Alprostadil. The process of example number 1 was applied for preparation. The drug Alprostadil (0.5 % w/w) was added simultaneously along with Prilocaine and Lidocaine by reducing the quantity of solvent.

Example 11:

The inventive composition of present invention was also successfully developed along with Tramadol. The solvent diethylene glycol monoethyl ether (25.41% w/w) and Tramadol (20 % w/w) along with Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) were mixed slowly together in solvent with continuous stirring for about 15 min. The further process was followed as per example 1. The propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 42.83 % w/w) was charged with pressure in to the canister.

Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 12:

Preparation of composition containing Feracrylum and adjuvant 3%w/w of Feracrylum is taken and dissolved in 14 % w/w of distilled water to which 8.82 % of w/w of Lignocaine & 2.94 % w/w of Prilocaine with 22 % w/w of isopropyl alcohol are also added and dissolved. This mixture is filtered and filled with a 49.24 % w/w of propellant and suitable fragrances and flavors to enhance the aesthetic appeal of the formulation, then sealed in a container.

Example 13:

The spray formulation with Absolute alcohol (32.5 % w/w) formulated by dissolving Lidocaine (6.5 % of w/w) & Prilocaine (1.5 % w/w) along with Ketamine (1.25% w/w) and then allowed to continuous stirring for about 15 min. Then menthol (5 % w/w) was added to the solution and stirred for 15 minutes to dissolve. The solution was then filled in to the aluminum canisters. Dip tube and metered valve are placed inside the canister. The filled canisters were crimped. Further the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 53.24 % w/w) was charged with pressure in to the canister. Actuator was placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 14:

The spray formulation formulated with absolute alcohol (27.5 % w/w) along with DEET (N, N-diethyl-m-toluamide (8 % w/w) by dissolving Lidocaine (8.82 % of w/w) & Prilocaine (2.94 % w/w) with continuous stirring for about 15 min and butylated hydroxytoluene (0.05 % w/w) added and dissolved. Then menthol (5 % w/w) was added to the solution and stirred for 15 minutes to dissolve. The solution was then filled in to the aluminum canisters. Dip tube and metered valve are placed inside the canister. The filled canisters were crimped. Further the propellant 1,1,1,2 Tetrafluoroethane in appropriate quantity (about 47.70 % w/w) was charged with pressure in to the canister. Actuator was

placed on the canister and the aerosol canister was closed with suitable cap. Suitable fragrances and flavors were added optionally to enhance the aesthetic appeal of the formulation.

Example 15:

The spray dosage form was also formulated with active principles of extracts derived from the mucuna pruriens. The process of example 1 was applied for preparation. The 25 % w/w active principles of mucuna pruriens was added simultaneously along with 5% w/w Prilocaine and 15% w/w Lidocaine by reducing the quantity of solvent.

Data of Clinical Evaluation:

The present novel composition and its application with an inventive step have motivated the present inventors to perform the clinical trial on cited example.

It is evident that, none of the prior arts have proven its beneficial composition which is useful for the claim indications. The applicants were motivated to perform the clinical trial on cited examples and composition.

The clinical trial was performed by granted protocol approved by regulatory agency and as per approved guidelines.

Clinical study has been conducted to evaluate the efficacy and safety of topical metered dose spray formulation containing Lidocaine and Prilocaine and pharmaceutical acceptable active ingredients. The effects of the topical composition was compared with the effects of placebo between two groups of patients suffering from premature ejaculation in the age group of 20-52 years by evaluating parameters such as intravaginal ejaculatory latency time and conditions alike. The composition was administered locally as per the clinical trial protocol on glans penis of 120 patients suffering from pathology of premature ejaculation. The clinical outcome of the formulation of the present invention gave surprisingly good response in target patient groups.

Results are summarized below:

COMPARISON OF CHANGES IN MEAN INTRAVAGINAL EJACULATORY LATENT TIME BETWEEN TWO GROUPS

Duration in Weeks	Mean IELT (secs) ($\bar{X} \pm SD$)	
	Lignocaine + Prilocaine	Placebo
Baseline	032.24 ± 06.85	30.58 ± 10.26
1	@ *079.67 ± 20.88	*34.95 ± 11.30
2	@ *115.31 ± 26.20	*40.69 ± 09.11
3	@ *128.32 ± 27.85	*50.85 ± 20.48
4	@ *165.66 ± 29.08	*48.36 ± 19.22
5	@ *180.31 ± 31.58	*54.32 ± 10.30
6	@ *192.95 ± 34.95	*52.30 ± 09.67
7	@ *210.30 ± 41.00	*54.33 ± 18.67
8	@ *235.58 ± 49.42	*59.88 ± 23.26

By ANOVA *P < 0.05 Significant

@Betn Grps P < 0.05 Significant

Above table shows that mean IELT was **32.24** secs in Lignocaine + Prilocaine group and **30.58** secs among Placebo group at baseline which was same and difference was not statistically significant.

In view of the above results, it is concluded that, the present invention of the spray formulation composition comprising Lidocaine and Prilocaine was found to be very effective in the patients suffering from premature dysfunction/ejaculation. It was found to be safe and tolerated and no serious adverse reactions were reported by any patient as well as no significant changes in hematological and biochemical parameters occurred after the course of Lidocaine and Prilocaine spray formulation.

We claim,

1. A topical pharmaceutical composition comprising Lidocaine or its pharmaceutically acceptable salts in combination with one or more other local anesthetic agent(s) along with propellants, solvents and other pharmaceutically acceptable excipient(s), useful for the treatment of premature ejaculation and like conditions optionally with additional therapeutic active ingredient(s).

2. The topical composition according to claim 1, wherein said composition comprises Lidocaine or its pharmaceutically acceptable salts and Prilocaine or its pharmaceutically acceptable salts along with propellants, solvents and other pharmaceutically acceptable excipients.

3. The topical composition according to claim 1, wherein other pharmaceutically acceptable excipient(s) are selected from Penetration enhancers, spreading agents, viscosity increasing agents, surfactants or suspending agents, pH modifying agents, moistening agents or humectants, adjuvants, rheology modifiers, Corrosion inhibitors, Soothing agents, vehicles or diluents or bulking agents, anti-oxidants, chelating agents, emollients, emulsifiers, preservatives and evaporation retardants alone or in combination.

4. The topical composition according to claim 1, wherein said composition is in the form of metered dose spray.

5. The topical composition according to claim 1, wherein said pharmaceutical active ingredients are present in an amount of 5 to 50 % by weight concentration.

6. The topical composition according to claim 1, wherein lidocaine is present in an amount of 5 % to 15 % by weight and Prilocaine is present in an amount of 1 % to 4 % by weight in concentration.

7. The topical composition according to claim 2, wherein the Lidocaine and Prilocaine are mixed together in ratio of 5:95 to 95:5.

8. The topical composition according to claim 1, wherein the excipient(s) used is present in an amount of 10 % to 95 % by weight in concentration.

9. The topical composition according to claim 1, wherein said propellant is 1,1,1,2 Tetrafluoroethane, present in an amount of 30 % to 70% by weight in concentration.

10. The topical composition according to claim 1, wherein said solvent used is diethylene glycol monoethy ether, present in an amount of 20 to 40 % w/w.

11. The topical composition according to claim 1, wherein said composition is in the form of an emulsion, lotion, paste, gel, cream, ointment, suspension, solution, balm, salve, foam or pump spray.

12. The topical composition according to claim 1, wherein said composition further comprises of therapeutic active agent(s) selected from group of antidepressant, Selective serotonin reuptake inhibitors (SSRI), Serotonin-norepinephrine reuptake inhibitor (SNRI), Phosphodiesterase type 5 (PDE5) inhibitor, Haemostatic agents, analgesic, antipyretic, Non-steroidal anti-inflammatory, Anti-histaminic, Vasodilators, Antimicrobial agents, N-methyl d-Aspartate (NMDA) receptor antagonist, Cytochrome P450 inhibitor, Serotonin agonist, Serotonin antagonist, Adrenergic antagonist, Adrenergic neurone blocker categories and herbal extracts.

13. The topical composition according to claim 1 and 9, wherein herbal extract are selected from extracts of *Mucuna pruriens, Ginseng redix alba, Angelicae gigantic radix, Cistanchis herba, Zanthoxylli fructs, Torlidis semen, Asiasari radix, Caryophylli flos, Cinnamoni cortex,* and *Bufonis veneum, Abrus precatorius linn.*

14. A metered dose spray dispenser to deliver the composition of claim 1.

15. Method of treating symptoms associated with premature ejaculation, which comprises administering 'an effective amount' of the 'topical pharmaceutical composition' according to claim 1 to the subject suffering related symptoms, wherein the said topical pharmaceutical composition comprise of Lidocaine or its pharmaceutically acceptable salts in combination with one or more other local anesthetic agent(s) along with propellants, solvents and other pharmaceutically acceptable excipient(s).

16. The method according to claim 15, wherein said subject is human.

17. Use of 'topical pharmaceutical composition' of claim 1, for treatment of premature ejaculation and like conditions.