

VAGINAL PHARMACEUTICAL COMPOSITION COMPRISING MICONAZOLE AND LULICONAZOLE OR SALTS THEREOF

FIELD OF THE INVENTION

5 The present invention relates to a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts for the treatment of vaginal infections.

Particularly, the present invention relates to a vaginal pharmaceutical composition for treating vaginal infections and process of preparation thereof.

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More particularly, the present invention relates to a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts and at least one pharmaceutically acceptable excipient and its preparation process and method of using the same for the treatment of vaginal infections.

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BACKGROUND OF THE INVENTION

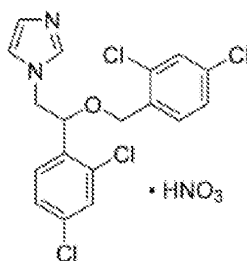
Vaginal yeast infection is a common fungal infection of the genitals. Approximately 20% of women get an infection yearly. About 75% of women have at least one infection in their lifetime. Vulvovaginal candidiasis is a relatively common form of yeast infection. Yeast infections also termed Candidiasis, Moniliasis, or Monilia vaginitis are among the most frequently occurring of vaginal infections. These vaginal infections are caused by fungus-like yeasts of the genus *Candida* (formerly *Monilia*), and specifically the species including *C. albicans*, *C. tropicalis*, *C. psuedotropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, as well as *Bacteroides fragilis* and *Gardnerella vaginalis*. Generally, 90% yeast infections caused by *Candida albicans*.

These *Candida* fungal microorganisms normally grow and thrive at low concentrations in the mouth, gastrointestinal tract, and vagina, coexisting with the normal biological flora in these regions, without adverse effect on health or physiological function. *Lactobacillus* bacteria keep its growth in check. But if there's an imbalance in system, these bacteria won't work effectively. This leads to an overgrowth of yeast, which causes the symptoms of vaginal yeast infections such as vaginal itching, swelling around the vagina, burning during urination or sex, pain during sex, soreness, redness, rash and vaginal discharge.

The types of vaginal infections are yeast infections, bacterial vaginosis, trichomoniasis, a sexually transmitted infection (STIs), chlamydia or gonorrhea, viral vaginitis (herpes), trichomoniasis, non-infectious vaginitis and atrophic vaginitis.

5 For intravaginal treatment various types of tablets, capsules, foams, pessaries, ointments and creams containing various conventional drugs in conventional delivery systems have been introduced for either short or long term therapy. More effective treatment of Candida infections typically involves the application of an anti-yeast medication to the vagina, with intravaginal administration of medicine being repeated at selected intervals over a period of
10 days or weeks.

Miconazole nitrate is an imidazole synthetic antifungal agent. It selectively affects the integrity of fungal cell membranes. Chemically Miconazole nitrate is 1-[2, 4-dichloro-β-
15 {(2,4-dichlorobenzyl)oxy} phenethyl] imidazole mononitrate and its molecular weight is of 479.15. Its empirical formula is $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$. Miconazole nitrate is represented by compound of structural formula I.



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Formula I

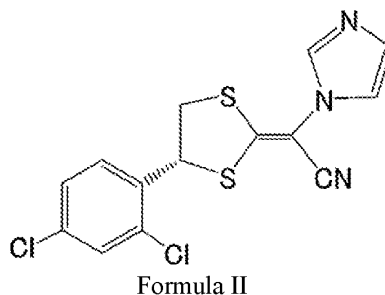
Miconazole nitrate is a white to almost white powder. It is soluble in water and organic solvents such as ethanol, DMSO and dimethyl formamide (DMF), propylene glycol or pyridine.

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Miconazole nitrate vaginal cream 2% and 4% was approved in USA on Feb 15, 1991 and Mar 30, 1998 under the trade name “MONISTAT 7” and “MONISTAT 3” respectively and was indicated for the treatment of vaginal yeast infections and relieves external itching and irritation associated with it.

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Luliconazole is an imidazole antifungal drug. Chemically Luliconazole is (2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile. Luliconazole is the R enantiomer and contains one chiral center. The double bond adjacent to the dithiolane group is in the E configuration. Its molecular weight is of 354.28. Its empirical formula is C₁₄H₉Cl₂N₃S₂. Luliconazole is represented by compound of structural formula II.



Luliconazole is a light yellow to yellow solid. It is low soluble in water, soluble in Acetonitrile, Dimethyl sulfoxide and slightly soluble in Chloroform and Methanol.

Luliconazole topical cream (1%) was approved in USA on Nov 14, 2013 under the trade name “Luzu” and is indicated for the treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

U.S. Patent No. 10086008 discloses topical paste comprising one or more antifungal agents, excipient inert powder and pharmaceutically acceptable topical carrier. This patent application generically discloses antifungal agent such as clotrimazole, ketoconazole, miconazole, oxiconazole, econazole, luliconazole, terbinafine, nystatin, fluconazole, voriconazole, itraconazole, caspofungin, micafungin, naftifine, butenafine, amorolfine, ravuconazole, posaconazole, flucytosine, sertaconazole, efinaconazole, enilaconazole, saperconazole, sulconazole, terconazole, tioconazole, nikkomycin Z, anidulafungin (LY303366), pimarin, griseofulvin, haloprogin, tolnaftate, undecylenate, or any combination thereof. Further this patent application specifically discloses terbinafine or terbinafine hydrochloride containing antifungal composition; however it does not teaches or discloses vaginal composition of Miconazole and Luliconazole.

U.S. Patent No. 5514698 discloses a long-lasting viscous antifungal vaginal cream composition comprising an imidazole antifungal drug from miconazole, econazole, terconazole, saperconazole, itraconazole, ketoconazole, and clotrimazole; however it does not teaches or discloses vaginal composition of Miconazole and Luliconazole.

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PCT Publication No. WO2011121604 discloses liquid vaginal spray dosage form comprising therapeutically effective amount of at least one antifungal agent along with lactic acid; wherein antifungal agent is selected from Miconazole, Ketoconazole, Clotrimazole, Econazole, Bifonazole, Butoconazole, Fenticonazole, Isoconazole, Oxiconazole, Sertaconazole, Sulconazole, Tioconazole, Griseofulvin, Fluconazole Fosfluconazole, Itraconazole, Posaconazole, Voriconazole, Amorolfine, Butenafine, Naftifine, Terbinafine, Terbinafine, Natamycin, Nystatin, Amphotericin B, Thiabendazole, Anidulafungin, Caspofungin, Micafungin, Flucytosine; however it does not teaches or discloses vaginal composition of Miconazole and Luliconazole.

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Currently, commercially available marketed product in the vaginal fungal infection treatment includes Butoconazole Nitrate as vaginal cream 2%, Clotrimazole as Topical cream 1%, Miconazole as vaginal cream 4%, suppository of 100mg and 200mg strength, Terconazole as cream in 0.4%, 0.8% strength and also as suppository of 80mg strength, Fluconazole as tablet in 50mg, 100mg, 150mg, 200mg strengths.

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The most common adverse effect of product known in the prior art for Luliconazole is application site reactions and for Miconazole are allergic contact dermatitis, cellulitis, irritation, burning, maceration; therefore, these product does not provide patient compliance in the treatment of vaginal fungal infection.

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In the marketed products there is no combination of Miconazole and Luliconazole is available, hence there is unmet need to develop a vaginal pharmaceutical composition comprising combination of Miconazole or its salts and Luliconazole or its salts.

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Vaginal infections are very common, because there are many factors that can interfere with the vaginal flora, which reduces vaginal resistance to infection, such as but not limited to bacterial and fungal infections. Therefore, it has important clinical significance for the

prevention and treatment of reproductive tract infections if it inhibits harmful bacteria and fungi.

Therefore, there is an unmet need in the art to develop a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole and Luliconazole with minimum adverse effects, with broad spectrum of antifungal activity, which is efficient and provides better patient compliance in the treatment of vaginal fungal infection.

Accordingly, applicant of the present invention invented a novel vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts which is efficient, having broad spectrum of activity against vaginal infections with minimum adverse effect and better patient compliance.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts with one or more of pharmaceutically acceptable excipient.

It is an object of the present invention to provide a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts.

It is an object of the present invention to provide a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with one or more of pharmaceutically acceptable excipient.

It is an object of the present invention to provide a vaginal pharmaceutical composition for treating vaginal infections, comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- ii) 0.01-5 % w/w of Luliconazole or its salts;
- iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- vii) q.s of vehicle.

It is an object of the present invention to provide a vaginal pharmaceutical composition, comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- 5 ii) 0.01-5 % w/w of Luliconazole or its salts;
- iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- 10 vii) q.s of vehicle.

It is further object of the present invention to provide a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with broad spectrum of antifungal activity in the treatment of vaginal fungal infection.

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A further object of the invention is to provide a process for the preparation of a vaginal pharmaceutical composition, comprising Miconazole or its salts and Luliconazole or its salts, comprising:

- (a) Aqueous phase: dissolving preservative in purified water, mixing and heating at suitable temperature;
- 20 (b) Lipid phase: Mixing co-emulsifier, emulsifier, lubricant and preservative and heating at suitable temperature;
- (c) Cooling the lipid phase of step (b) at suitable temperature and mixing both active pharmaceutical ingredients (APIs) for 5-10 minutes;
- 25 (d) Emulsification is achieved by adding step (c) to step (a), mixing for 10 minutes; and
- (e) cream obtained in step (d) is mixed slowly and allow to cool down at room temperature.

SUMMARY OF THE INVENTION

A main aspect, the present invention discloses a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.

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In one aspect, the present invention discloses a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts.

In another aspect, the present invention relates to a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.

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In another aspect, the present invention relates to a vaginal pharmaceutical composition for treating vaginal infections, comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- ii) 0.01-5 % w/w of Luliconazole or its salts;
- 10 iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- vii) q.s of vehicle

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In another aspect, the present invention relates to a vaginal pharmaceutical composition, comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- ii) 0.01-5 % w/w of Luliconazole or its salts;
- 20 iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- vii) q.s of vehicle

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In another aspect, the present invention provides a process for the preparation of a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts, comprising:

- (a) Aqueous phase: dissolving preservative in purified water, mixing and heating at suitable
- 30 temperature;
- (b) Lipid phase: Mixing co-emulsifier, emulsifier, lubricant, and preservative and heating at suitable temperature;
- (c) Cooling the lipid phase of step (b) at suitable temperature and mixing both active pharmaceutical ingredients (APIs) for 5-10 minutes;

(d) Emulsification is achieved by adding step (c) to step (a), mixing for 10 minutes; and
(e) cream obtained in step (d) is mixed slowly and allow to cool down at room temperature.

In another aspect of the present invention is to provide a vaginal pharmaceutical composition
5 for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts.

DETAIL DESCRIPTION OF THE INVENTION

The term "composition" or "pharmaceutical composition" or "vaginal pharmaceutical
composition" or "topical pharmaceutical composition" as used herein synonymously include
10 dosage forms such as topical, cream, ointment or the like.

The term "infection" or "vaginal infections" or "fungal infections" or "yeast infections" or
"Vaginal yeast infections" or "vaginal fungal infection" as used herein synonymously.

15 In the following specification and the claims, reference will be made to a number of terms,
which shall be defined to have the following meanings. The singular forms "a", "an", and
"the" include plural references unless the context clearly dictates otherwise.

The present invention relates to vaginal pharmaceutical composition comprising Miconazole
20 or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable
excipient.

The present invention relates to vaginal pharmaceutical composition for treating vaginal
infections comprising Miconazole or its salts and Luliconazole or its salts.

25 The Miconazole and Luliconazole of the present inventions may be present in the form of
free base or its pharmaceutically acceptable salt.

The term "Miconazole" is used in broad sense to include not only "Miconazole" per se but
30 also its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, derivatives,
isomers, polymorphs, prodrugs thereof and also its various crystalline and amorphous forms.

The salts of Miconazole may be selected from nitrate, maleate, hemifumarate, hemisuccinate
and the like; preferably Miconazole nitrate salt is used.

The concentration of Miconazole or its salts is at least 0.1%; preferably range from 0.1% to 10%; more preferably from 0.25% to 5% by total weight of composition.

- 5 The term “Luliconazole” is used in broad sense to include not only “Luliconazole” per se but also its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, derivatives, isomers, polymorphs, prodrugs thereof and also its various crystalline and amorphous forms.

- 10 The salts of Luliconazole may be selected from formic acid, acetic acid, citric acid, tartaric acid, bitartaric acid, benzoic acid, lactic acid, malic acid, fumaric acid, succinic acid, gluconic acid, pamoic acid, methanesulfonic acid, benzenesulfonic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, phosphoric acid, sulfuric acid, trifluoroacetic acid or the like.

- 15 The concentration of Luliconazole or its salts is at least 0.01%; preferably ranges from 0.01 to 5%; more preferably from 0.1% to 4% by weight of the composition.

- 20 The term “fungal infection” as used in the present invention can be selected from the group of vaginal candidiasis (candida) or moniliasis, or monilia vaginitis, caused by fungus-like yeasts of the genus *Candida* (formerly *Monilia*), and fungal infections caused specifically by the species including *C. albicans*, *C. tropicalis*, *C. psuedotropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei* and *C. stellatoidea*.

- 25 The vaginal infections as used in the present invention can be the groups of vaginal infections are yeast infections, bacterial vaginosis, trichomoniasis, a sexually transmitted infection (STIs), chlamydia or gonorrhea, viral vaginitis (herpes), trichomoniasis, non-infectious vaginitis and atrophic vaginitis.

- 30 Spectrum of antifungal activity of Miconazole nitrate includes many fungi, including yeasts and dermatophytes. It is particularly active against *Candida* spp. (*C. guilliermondii* and *C. tropicalis*), *Trichophyton* spp. (*Trichophyton mentagrophytes*, and *Trichophyton rubrum*), *Epidermophyton* spp. (*E. floccosum*), *Microsporum* spp. (*M. canis*), *Pityrosporon orbiculare* (*Malassezia furfur*) and other, but also possesses some activity against Gram-positive bacteria (*Staphylococcus aureus*).

Spectrum of antifungal activity of Luliconazole includes dermatophytes, yeasts, and some other fungi. It is particularly active against Trichophyton spp. (*T. rubrum*, *T. mentagrophytes* and *T. tonsurans*, *T. verrucosum*, *T. violaceum*, *Microsporum canis*, and *M. gypseum*,
5 *Epidermophyton floccosum*), *Candida albicans*, *Malassezia furfur*, *Malassezia restricta*, *Malassezia slooffiae*, and *Malassezia sympodialis* and other.

Miconazole and Luliconazole of present invention act as an antifungal which inhibit/prevent vaginal fungal infections.

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Miconazole acts by inhibiting the 14 α -demethylation of lanosterol, which consequently leads to the inhibition of ergosterol synthesis in fungal cell membranes. Additionally, Miconazole has been shown to induce reactive oxygen species in fungal biofilms, demonstrating a MIC value of $\geq 256\mu\text{M}$ against candida spp.

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Luliconazole acts by inhibiting the ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol.

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The vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts; wherein Miconazole or its salts and Luliconazole or its salts is providing potent antifungal activity, efficacy and patient compliance in the treatment of vaginal fungal infection.

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The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts according to present invention broaden the spectrum of activity, enhance the rate or extent of antifungal or antibacterial activity and reduce toxicities for the treatment of vaginal fungal infection.

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In one embodiment, the present invention provides a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.

In one embodiment, the present invention discloses a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts.

5 In one embodiment, the present invention discloses a vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.

The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts according to present invention is
10 formulated into a dosage form selected from a group comprising of pessary, vaginal ring, douche, suppository, tablet, soft capsule, tampon, foam, spray, gel, cream, Intrauterine device (IUD), ointment, paste, lotion, solution, tincture, powder, mousses, cleansers and mucoadhesive vaginal film or like thereof.

15 The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.

The vaginal pharmaceutical composition for treating vaginal infections comprising
20 Miconazole or its salts and Luliconazole or its salts may contain one or more pharmaceutically acceptable excipient selected from the group consisting of bases, emollients, lubricant, thickening agent or thickeners, surfactants, solubilizing or emulsifying agent or emulsifier, co-emulsifier, preservative, antioxidant, humectant, absorbent,
25 alkalizing or buffering agent, perfumes or fragrances, antifoaming agent, adherent agent, bioadhesive polymer, vehicle and any other excipient known to the art for making pharmaceutical composition.

The example of bases according to the present invention include but not limited to group
30 comprising of carnauba wax, cetyl alcohol, cetyl ester wax, emulsifying wax, hydrous lanolin, lanolin, lanolin alcohols, vegetable oils and animal fat; coconut oil, bees wax, olive oil, spermaceti wax, sesame oil, almond oil, alcohols, acids and esters; oleic acid, oleyl alcohol, palmitic acid, lauryl alcohol, lauric acid, myristyl alcohol, ethyl oleate, isopropyl myristicate, ethylene glycol, hydrogenated and sulphated oils; hydrogenated castor, cotton

seed, hydrogenated sulphated castor oils, microcrystalline wax, liquid paraffin, petrolatum, polyethylene glycol, stearic acid, stearyl alcohol, white wax, yellow wax or combination thereof.

- 5 The examples of emollients according to the present invention include but not limited to group comprising of waxes, fats, caprylic/capric triglycerides, castor oil, cetareth-20, cetareth-30, cetaryl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, di-isopropyladipate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white
10 petrolatum, polyethylene glycol, polyoxyethylene glycol fatty alcohol ethers, polyoxypropylene 15-stearyl ether, propylene glycol stearate, squalane, steareth-2 or -100, stearic acid and urea, oils of natural origin such as almond oil, coconut oil, olive oil, palm oil, peanut oil and the like, fatty acids such as lauric acid, myristic acid, palmitic acid, and stearic
15 acid, monohydric alcohol esters of the fatty acids such as ethyl laurate, isopropyl laurate, ethyl myristate, n-propyl myristate, ethyl palmitate, methyl palmitate, methyl stearate, ethyl stearate, isopropyl stearate, butyl stearate, isobutyl stearate, amyl stearate, and isoamyl stearate, glycols such as ethylene glycol, diethylene glycol, polyethylene glycol, branched aliphatic alcohols such as lauryl alcohol, myristyl alcohol, and stearyl alcohol or combination
20 thereof.

The examples of lubricant according to the present invention include but not limited to group comprising of castor oil, mineral oil, paraffin oil, ispagol mucilage, vitamin D, talc or any mixture thereof. The amount of lubricant present in the composition may ranges from about
25 0.1-15%; preferably about 0.5-12%; more preferably about 1-10% by weight of composition.

The examples of thickening agent or thickeners according to the present invention include but not limited to group comprising of carbomer, hydrogenated castor oil, methyl cellulose, sodium carboxyl methyl cellulose, carrageenan, colloidal silicon dioxide, natural gum such as
30 gelatin, tragacanth gum and guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene oxide, alginic acid, paraffin, cetostearyl alcohol, PEG 200, PEG 300, PEG 400, PEG 600, monoethanolamine, triethanolamine, glycerol, propylene glycol, polyoxyethylene sorbiton monoleate, and poloxamers, polyvinyl pyrrolidone, various

alcohols such as polyvinyl alcohol, ethanol or isopropyl alcohol, fumed silica or combination thereof.

The examples of surfactant according to the present invention include but not limited to group comprising of ionic, cationic and non-ionic surfactants or the like or any mixture thereof, further one or more of surfactant selected from but not limited to polysorbate, polysorbate 20, polysorbate 40, polysorbates 80, polysorbate 60, poloxamer, sorbitan monostearate, sorbitan monooleate, sodium lauryl sulfate, propylene glycol monostearate, dodecyl benzene sulfonate, polyethylene glycol, PEG 100 stearate polyethylene glycol 6000 distearate, polyethylene glycol 1000 monocetyl ether, polyethylene glycol monostearate, polyethylene glycol 400 monostearate, polyoxyethylene glycol fatty alcohol ethers, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, PPG-26 oleate, sorbitan esters, sorbitan monolaurate, sorbitan monopalmitate, sorbitan palmitate, sorbitan sesquioleate, or the like or combination thereof.

the examples of solubilizing or emulsifying agent or emulsifier according to the present invention include but not limited to group comprising of apricot kernel oil PEG-6 ester, pegoxol-7 stearate, polysorbate 20, polysorbate 80, polysorbate 60, poloxamer, emulsifying wax, sorbitan monostearate, sorbitan monooleate, sodium lauryl sulfate, propylene glycol monostearate, natural gums like acacia and tragacanth, monovalent and bivalent soaps, lanolin, cholesterol or cholesterol esters, triethanolamine and its salts, dodecyl benzene sulfonate, diethylene glycol monoethyl ether, docusate sodium or mixture thereof. the amount of solubilizing or emulsifying agent or emulsifier present in the composition ranges from about 0.1-25%; preferably 1 to 22% by weight of composition.

The examples of co-emulsifier according to the present invention include but not limited to group comprising of apricot kernel oil PEG-6 ester, propylene glycol stearate, cetyl hydroxyethyl cellulose, poloxamer 407, polyglyceryl-2 stearate or combination thereof. the amount of co-emulsifier present in the composition ranges from about 0.1-10%; preferably 0.05 to 8% by weight of composition.

The example of preservative according to the present invention include but not limited to group comprising of chorocresol, benzoic acid, butylated hydroxyanisole, phenyl mercuric nitrate, benzyl alcohol, benzoic acid and its salts, boric acid, methyl paraben, propyl paraben,

trihydrate and anhydrous sodium acetate, chlorhexidine, formaldehyde, glutaraldehyde, imidazolidinyl urea, trichlosan, benzalkonium chloride, chloroxylonol or combination thereof. the amount of preservative present in the composition may ranges from about 0.001-6%; preferably about 0.001-5%; more preferably about 0.005-4.5% by weight of composition.

The example of antioxidant according to the present invention include but not limited to group comprising of butylated hydroxylanisole, butylated hydroxyl toluene, propyl gallate, polyols like sorbitol, xylitol and maltitol, natural extracts like quillaia, or lactic acid or urea, lithium chloride, ascorbic acid, sodium metabisulfite, carotinoids, carotenes such as α -carotone, β -carotene and lycopene, chlorogenic acid, tocopherols, uric acid, zno, znso₄ or combination thereof.

The example of humectant according to the present invention include but not limited to group comprising of glycerin, glyceryl triacetate, propylene glycol, polyethylene glycol, sorbitol solution, 1,2,6 hexanetriol, isopropyl myristate, petrolatum, isopropyl palmitate, hydrogenated castor oil, mineral oil, polyoxymethylene urea, potassium sorbate or combination thereof.

The example of absorbent according to the present invention include but not limited to group comprising of magnesium carbonate, calcium carbonate, starch, cellulose and its derivatives or combination thereof.

The example of permeation enhancer according to the present invention include but not limited to group comprising of propylene glycol, ethanol, isopropyl alcohol, oleic acid, polyethylene glycol, phospholipids, cyclodextrins, black pepper (piper nigrum), pyrrolidones, dimethyl sulphoxide (dmso), decylmethyl sulphoxide (dcms), terpenes (cineole, eugenol, d-limonene, menthol, menthone), urea or combination thereof.

The examples of opacifying agent according to the present invention include but not limited to group comprising of higher fatty alcohols such as cetyl, stearyl, cetostearyl alcohol, arachidyl and behenyl alcohols, solid esters such as cetyl palmitate, glyceryl laurate, various fatty acid derivatives such as propylene glycol and polyethylene glycol esters, inorganic

materials such as, magnesium aluminum silicate, zinc oxide, titanium dioxide or other sunblocking agents or combination thereof.

5 The example of chelating agent according to the present invention include but not limited to group comprising of ethylene diamine tetraacetate, dimercaprol, dimercaptosuccinic acid, penicillamine, deferoxamine, deferasirox, citric acid, maleic acid, phosphoric acid or combination thereof.

10 The example of gelling agent according to the present invention include but not limited to group comprising of carbomer/carbopols, pemulen®, cellulose derivatives such as methyl cellulose, hydroxy ethylcellulose, hydroxy propylmethylcellulose, carboxy methyl cellulose, hydroxy propyl cellulose, etc., glycerol, or propylene glycol gelled with suitable agents such as natural gums such as xanthan gum and tragacanth, fenugreek mucilage, pectin, poloxamers (pluronics), alginate, gelatin, starch, polyvinyl alcohol, povidone or combination thereof.

15 The example of acidifying or alkalizing or buffering agent according to the present invention include but not limited to group comprising of anhydrous and monohydrate citric acid, phosphoric acid, sodium hydroxide, potassium hydroxide, sodium bicarbonate, potassium sorbate, monobasic and dibasic sodium phosphate, trolamine or combination thereof.

20 The example of perfume or fragrances according to the present invention include but not limited to group comprising of lavender, lemon, gardenia, hypo allergenic perfume, menthol or combination thereof.

25 The example of antifoaming agent according to the present invention include but not limited to group comprising of cyclomethicone, dimethicone and simethicone or combination thereof.

30 The example of adherent agent according to the present invention include but not limited to group comprising of natural gum (arabic, align, guar, tragacanth and xanthan gums, pectin and dextran) or combination thereof.

The example of bioadhesive polymer according to the present invention include but not limited to group comprising of ethyl cellulose, polyvinylpyrrolidone, hydroxyl propyl methyl

cellulose, hydroxyl propyl cellulose, hydroxyl ethyl cellulose, ethyl cellulose or combination thereof.

The example of vehicle according to the present invention include but not limited to group
5 comprising of purified water, hexylene glycol, propylene glycol, oleyl alcohol, propylene
carbonate, mineral oil, almond oil, cottonseed oil, ethyl oleate, isopropyl myristate, isopropyl
palmitate, myristyl alcohol, octyldodecanol, olive oil, peanut oil, safflower oil, sesame oil,
soybean oil, squalene, polyethylene glycol, diethylene glycol monoethyl, glycofurol, benzyl
10 alcohol, labrasol, benzyl benzoate and ethyl oleate, diethylene glycol monoethyl ether, ethyl
alcohol, cremophore ELP, solutol, transcitol, capmul, captex or mixture thereof. Preferably
the vehicle is water. The vehicle according to present invention may be present in an amount
to make up volume to quantity sufficient.

In one embodiment, the present invention provides a vaginal pharmaceutical composition for
15 treating vaginal infections, comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- ii) 0.01-5 % w/w of Luliconazole or its salts;
- iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- 20 v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- vii) q.s of vehicle

In one embodiment, the present invention provides a vaginal pharmaceutical composition,
25 comprising:

- i) 0.1%-10 % w/w of Miconazole or its salts;
- ii) 0.01-5 % w/w of Luliconazole or its salts;
- iii) 0.1-15 % w/w of lubricant;
- iv) 0.1-25 % w/w of emulsifier;
- 30 v) 0.1-10 % w/w of co-emulsifier;
- vi) 0.001-6% w/w of preservative; and
- vii) q.s of vehicle

In one embodiment, the present invention provides a process of preparation of a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts, comprising:

- 5 (a) Aqueous phase: dissolving preservative in purified water, mixing and heating at suitable temperature;
- (b) Lipid phase: Mixing co-emulsifier, emulsifier, lubricant, and preservative and heating at suitable temperature;
- (c) Cooling the lipid phase of step (b) at suitable temperature and mixing both active pharmaceutical ingredients (APIs) for 5-10 minutes;
- 10 (d) Emulsification is achieved by adding step (c) to step (a), mixing for 10 minutes; and
- (e) cream obtained in step (d) is mixed slowly and allow to cool down at room temperature.

The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salt and Luliconazole or salts, wherein said vaginal pharmaceutical
15 composition can be applied at least once a day or as per instructions of healthcare provider.

The vaginal pharmaceutical composition according to present invention can be applied to affected part through hand or suitable applicator.

- 20 The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or salts comprises other pharmaceutically acceptable polymers mainly used for to maintain proper viscosity of formulation.

The vaginal pharmaceutical composition for treating vaginal infections comprising
25 Miconazole or its salts and Luliconazole or its salts according to present invention may be manufactured by trituration method, levigation method, fusion method, chemical reaction method, emulsification method, cold method, dispersion method, moulding, compression, hand rolling and shaping, pour moulding, wet granulation, dry granulation or direct compression.

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The concentration of active ingredient Miconazole or its salts and Luliconazole or its salts and other excipients, manufacturing process has been optimized in way such that composition will have maximum therapeutic efficacy in the treatment of vaginal fungal infection with minimum or no side effects and which results in better patient compliance.

The synergism of Miconazole or its salts and Luliconazole or its salts according to present invention broaden the spectrum of activity, enhance the rate or extent of antifungal or antibacterial activity, and reduce toxicities in the treatment of vaginal fungal infection.

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The vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts is evaluated by determination of pH, primary skin irritation test, visual appearance, viscosity, spreadability, stability studies, rheological studies, thermal behavior, saponification value and acid value.

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The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts according to present invention may be loaded for stability studies as per ICH guidelines.

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The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts according to present invention may be packaged in to the collapsible tubes, jars, pot, bottle or single dose packets. The container material or packaging material of the present invention does not affect the quality of the preparation or does not allow diffusion of any kind into or across the material of the container into the preparation.

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The vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts according to present invention may be labeled according to the requirement under Good Manufacturing Practice.

25

The following examples serve to illustrate the embodiments of the present invention. However, they do not intend to limit the scope of the invention.

Example 1: Cream base approach:

Sr. No.	Ingredients	% w/w
1.	Miconazole nitrate	2.0
2.	Luliconazole	1.0
3.	Mineral oil	6.0

4.	Apricot kernel oil PEG-6 Ester	2.0
5.	Pegoxol-7 Stearate	14.0
6.	Butylated hydroxyanisole	0.015
7.	Benzoic Acid	0.25
8.	Purified water	q.s to 100

q.s.: Quantity sufficient

Manufacturing Process:

1. Aqueous phase: Benzoic Acid was dissolved in purified water, mixed and heated at 65-75°C;
- 5 2. Lipid phase: Apricot kernel oil PEG-6 Ester, Pegoxol-7 Stearate, Mineral oil, Butylated hydroxyanisole mixed and heated at 65-75°C;
3. Step 2 phase was allowed to cool at 65°C and both active pharmaceutical ingredients (APIs) Miconazole nitrate and Luliconazole were mixed for 5-10 minutes;
4. Emulsification was achieved by addition of step 3 to step 1, mixed for 10 minutes, and
- 10 5. Manufactured cream was mixed slowly and allowed to cool down at Room temperature.

Physical Parameters:

Sr. No.	Parameters	Observations
1.	Description	White- off white colored, homogenous uniform cream with smooth texture
2.	pH	3.50-5.00
3.	Viscosity	1000-3000 cPs

Example 2: Cream base approach with change in emulsifier and preservative:

Sr. No.	Ingredients	% w/w
1.	Miconazole nitrate	1.0
2.	Luliconazole	0.5
3.	Mineral oil	6.0
4.	Apricot kernel oil PEG-6 Ester	2.0
5.	Pegoxol-7 Stearate	14.0
6.	Butylated hydroxyanisole	0.015
7.	Benzoic Acid	0.25
8.	Purified water	q.s to 100

q.s.: Quantity sufficient

Manufacturing process:

1. Aqueous phase: Benzoic Acid was dissolved in purified water, mixed and heated at 65-75°C;
2. Lipid phase: Apricot kernel oil PEG-6 Ester, Pegoxol-7 Stearate, Mineral oil, mixed and heated at 65-75°C;
3. Step 2 phase was allowed to cool at 65°C and both active pharmaceutical ingredients (APIs) Miconazole nitrate and Luliconazole were mixed for 5-10 minutes;
4. Emulsification was achieved by addition of step 3 to step 1, mixed for 10 minutes, and
5. Manufactured cream was mixed slowly and allowed to cool down at Room temperature.

Physical Parameters:

Sr. No.	Parameters	Observations
1.	Description	White- off white colored, homogenous uniform cream with smooth texture
2.	pH	3.50-5.00
3.	Viscosity	1000-3000 cPs

We Claim:

1. A vaginal pharmaceutical composition for treating vaginal infections comprising Miconazole or its salts and Luliconazole or its salts with one or more pharmaceutically acceptable excipient.
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2. The vaginal pharmaceutical composition for treating vaginal infections as claimed in claim 1, wherein the vaginal pharmaceutical composition comprises:
 - i) 0.1%-10 % w/w of Miconazole or its salts;
 - 10 ii) 0.01-5 % w/w of Luliconazole or its salts;
 - iii) 0.1-15 % w/w of lubricant;
 - iv) 0.1-25 % w/w of emulsifier;
 - v) 0.1-10 % w/w of co-emulsifier;
 - vi) 0.001-6% w/w of preservative; and
 - 15 vii) quantity sufficient (q.s) of vehicle.
3. The vaginal pharmaceutical composition for treating vaginal infections as claimed in claim 1, wherein the vaginal infection is selected from a group comprising of yeast infections, bacterial vaginosis, trichomoniasis, a sexually transmitted infection (STIs), chlamydia or
20 gonorrhea, viral vaginitis (herpes), trichomoniasis, non-infectious vaginitis, atrophic vaginitis and the like.
4. A vaginal pharmaceutical composition comprising:
 - i) Miconazole or its salts;
 - 25 ii) Luliconazole or its salts; and
 - iii) one or more pharmaceutically acceptable excipients.
5. A vaginal pharmaceutical composition as claimed in claim 4, comprising:
 - i) 0.1%-10 % w/w of Miconazole or its salts;
 - 30 ii) 0.01-5 % w/w of Luliconazole or its salts;
 - iii) 0.1-15 % w/w of lubricant;
 - iv) 0.1-25 % w/w of emulsifier;
 - v) 0.1-10 % w/w of co-emulsifier;
 - vi) 0.001-6% w/w of preservative; and

vii) quantity sufficient (q.s) of vehicle.

6. The vaginal pharmaceutical composition as claimed in any one of claim 1 and 4, wherein one or more pharmaceutically acceptable excipient is selected from a group comprising of
5 bases, emollients, lubricant, thickening agent or thickeners, surfactants, solubilizing or emulsifying agent or emulsifier, co-emulsifier, preservative, antioxidant, humectant, absorbent, permeation enhancer, opacifying agent, chelating agent, gelling agent, acidifying or alkalizing or buffering agent, perfumes or fragrances, antifoaming agent, adherent agent, bioadhesive polymer and vehicle and the like or combination thereof.

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7. The vaginal pharmaceutical composition as claimed in claim 1 and 4, wherein the composition is formulated into a dosage form selected from a group comprising of pessary, vaginal ring, douche, suppository, tablet, soft capsule, tampon, foam, spray, gel, cream, Intrauterine device (IUD), ointment, paste, lotion, powder, solution, tincture, mousses,
15 cleansers and mucoadhesive vaginal film.

8. A process for preparation of a vaginal pharmaceutical composition comprising Miconazole or its salts and Luliconazole or its salts, comprising:

(a) Aqueous phase: dissolving preservative in purified water, mixing and heating at suitable
20 temperature;

(b) Lipid phase: Mixing co-emulsifier, emulsifier, lubricant and preservative and heating at suitable temperature;

(c) Cooling the lipid phase of step (b) at suitable temperature and mixing both active pharmaceutical ingredients (APIs) for 5-10 minutes;

25 (d) Emulsification is achieved by adding step (c) to step (a), mixing for 10 minutes; and

(e) cream obtained in step (d) is mixed slowly and allow to cool down at room temperature.

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