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(54) Title: ANTI-FUNGAL COMPOSITION AND A PROCESS FOR MANUFACTURING THE ANTI-FUNGAL COMPOSITION

(57) Abstract: A pharmaceutical composition comprising atleast one of various anti-fungal agents selected from the group of Imidazoles, Diazoles, Triazoles, Allylamines their derivatives and Polyenes, miscellaneous compounds viz., hydroxy pyridones like 2,5(1′S,6′R)-7-chloro-2′,-4,6-trimethoxy-6′-methylspiro[benzofuran-2(3H),1′-[2]cyclohexene]-3,4′-dione and Methyl(3-methylphenyl)-carbamothioic acid O-2-naphthalenylester and especially a-(2,4-Difluorophenyl)- a-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalene-methanamine hydrochloride in a selective carrier media of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives .The preparation is suitable for administered by paranteral, oral, local routes. The preparation in solution form can be directly administered or used in manufacture of tablet,suspension, drops, nail polish formulations and the like.

ANTI-FUNGAL COMPOSITION AND A PROCESS FOR MANUFACTURING THE ANTI-FUNGAL COMPOSITION

Technical Field:

This invention relates to anti-fungal pharmaceutical composition suitable for parenteral, oral or local administration involving various anti-fungal agents such as anti-fungal Azole, Triazole and Allylamines especially compounds like α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride and alike, useful for the treatment of fungal infections caused in animals including mammals and humans.

Background of Invention:

It is well known that Polyenes, Diazoles, Triazoles and Allylamine anti-fungal derivatives are used widely as Anti-fungal agents in the form of topical, oral and parenteral preparations, for eg., various-Azoles like 1-[(2-chlorophenyl)-diphenylmethyl]-1H-imidazole; 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole;1-[2-[(2-chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole;cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine; 1-[2-[(4-chlorophenyl)-methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; rel-1-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy]phenyl]-4-(1-ethylethyl)piperazine;1-[2-(2,4-dichlorophenyl)-2-[(2,6-dichloro-phenyl)methoxy]ethyl]1H-imidazole;(Z)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethanone O-[(2,4-dichlorophenyl)methyl]oxime; 1-([1,1'-biphenyl[-4-yl-phenylmethyl)-1H-imidazole;1-[2-[(7-chlorobenzo[b]thien-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole;1-[2-[[(4-chlorophenyl)methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole, which are used topically or orally;

Anti-fungal allylamine like N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride; (E)-N-methyl-N-(3-phenyl-2-propenyl)-1-naphthalenemethanamine;N-[[4-(1,1-dimethylethyl)phenyl]methyl]-N-methyl-1-naphthalenemethanamine, are also used topically or administered orally; Triazole anti-fungal like α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol; 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-4-dihydro-2-(1-methylpropyl)-3H-1,2,4-

triazol-3-one; (αR,βS)-α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-4-pyrimideethanol; 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile; 2,5-nhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl] phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)-D-threo-penitol, are used orally or topically or parenterally ;

Hydroxy pyridine like 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone,2-aminoethanol salt, polyenes like Nystatin and [1R(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E, 29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,-39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid; Methyl(3-methylphenyl)-carbamothioic acid O-2-naphthalenylester; (1′S,6′R)-7-chloro-2′,-4,6-trimethoxy-6′-methylspiro[benzofuran-2(3H),1′-[2]cyclohexene]-3,4′-dione, which are used either topically, orally or parenterally for the treatment of mycotic infections.

US Patent 4416682 describes α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and its use thereof as an anti-fungal agent.

US Patent Application 2001046478 (corresponding to EP 0515312) describes the anti-infective combination of two drugs for use in topical application in infection of toe nails and finger nails. In particular it deals with a combination of a topical and a systemic antimycotic and a physiologically acceptable lacquer base suitable for the treatment and prophylaxis of onychomycoses.

US Patent 4, 404,236 describes anti-fungal derivatives of 1,3-bis-triazoyl-2-propanol.

NZ 3, 315, 184 describes the use of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol for inhibiting the growth or cancer and viral infection.

Application No. WO 1,997US15987, 1997907 describes the anti-fungal combination therapy.

US Patent 4,404216 describes the α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and the use thereof as an anti-fungal agent.

There are several prior arts related to the anti-fungal N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride. WO2001EP00562 20000120 (EP 1259261), describes a pharmaceutical composition comprising of solid oral dosage forms of the compound and its rapid disintegration along with taste masking preparations. WO0211764 describes a topical application of the above drug using the laser beam technique for the treatment of fungus infection. WO 01/54675 A2 describes a pharmaceutical composition of the compound in emulsifiable or self-emulsifying oral formulations.WO 02/078648 A2 describes the topical application of the compound along with a second drug viz., Diclofenac or Indomethacin for the treatment of fungal infections.

US 19970952288, PCT/EP96/02022, WO96/35423 uses a combination of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride and α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol to treat resistant strains of mycoses.

WO 01/95890 A2 describes the oral administration of a pharmaceutical composition of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride comprising of Sustained Release dosage form.

The above state-of-art clearly reveal the continuing need for anti-fungal compositions for various end uses / applications such as oral, parenteral and topical. However, all such known forms of anti-fungal formulations presently available are found to involve complex manufacturing technique which make its difficult and cost-extensive to obtain.

In particular, anti-fungal such as α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol required to treat widely rampant and menacing infections caused due to mycoses has limitations in its use as the known methods of its preparation do not allow the compound to be solubilized in higher strengths for the therapeutic purpose as the solubility of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol in saline is at a maximum of about 8 mg/ml leading to difficulties in formulating preparations.

Likewise the other well known anti-fungal N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine- hydrochloride, an allylamine anti-fungal agent, has an inherent limited aqueous solubility of about ~6mg/ml. An emulsion form is known to be used along with a vehicle but this form has an inherent drawback viz., of limited solubility in aqueous media thus making it difficult to be easily formulated.

To overcome the drug resistance problems and achieve proper therapeutic compliance the anti-fungal actives such as α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine- hydrochloride is required in higher concentrations which cannot be provided due to limitations in solubility of the said α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine- hydrochloride.

Also the existing formulation of α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol is only available in the form of tablet/capsule requiring cumbersome powder technology to prepare the same. Some references show that the suspension preparation is administered orally by crushing the tablet and mixing the same with fruit juice to overcome the taste or the infusion is filled in the syringe for the oral application.

However, the formulation of tablet and low concentration infusion poses difficulty for the proper administration in case of debilated and pediatric/geriatric patients. These patients often shows poor drug compliance

There is thus need in the art to provide anti-fungal formulations such as α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine- hydrochloride with high concentrations of actives which would avoid problems of drug resistance and also favour effective treatment of fungal infections such as mycotic infections.

Also in view of the widespread fungal infections especially mycotic infections prevailing in tropical and under developed countries there is an ever increasing demand for such anti-fungal compositions which would be simple to obtain at affordable and cost-effective rates and at the same time suitable for oral, parenteral and local/topical administration for treating wide range of fungal/mycotic infections.

Objects of the Invention

It is thus the basic object of the present invention to provide for anti –fungal pharmaceutical compositions which would be simple and cost effective to obtain and serve as effective anti –fungal formulations to treat/eradicate various fungal/mycotic infections.

Another object of the present invention is to provide a simple and cost effective anti-fungal formulation, which would be simple to manufacture but would serve as a good anti –fungal preparations with good bio-availability and patient compliance.

Another object of the present invention is directed to provide a solution to the much required readily obtainable anti –fungal preparation, which would be safe and suitable for oral, parenteral as well as topical administration.

Yet further object of the present invention is directed to provide simple and cost-effective anti –fungal formulations suitable for oral, parenteral and topical application, which would be storage, stable.

Summary of the Invention

Thus according to the present invention there is provided an anti –fungal pharmaceutical composition comprising at least one anti –fungal agent selected from anti –fungal azoles, anti-fungal allylamines, anti-fungal hydroxy pyridines and anti-fungal polymers in a carrier media selected from 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives.

The anti –fungal azoles suitable for use can be selected from 1-[(2-chlorophenyl)-diphenylmethyl]-1H-imidazole;1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole; 1-[2-[(2-chloro-3-thienyl) methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine;1-[2-[(4-chlorophenyl)-methoxy]-2-(2,4-dichloro-phenyl)ethyl]-1H-imidazole; rel-1-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-ethylethyl)piperazine; 1-[2-(2,4-dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy]ethyl]1H-imidazole; (Z)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanoneO-[(2,4-dichlorophenyl) methyl]oxime; 1-([1.1'-biphenyl[-4-yl-phenylmethyl)-1H-imidazole; 1-[2-[(7-chlorobenzo[b]thien-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; 1-[2-[[(4-chlorophenyl)methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol; 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one; (αR,βS)-α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-4-pyrimideethanol; 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile; 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl] phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)-D-threo-penitol.

The anti-fungal allylamines suitable for use can be selected from N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride; (E)-N-methyl-N-

(3-phenyl-2-propenyl)-1-naphthalenemethanamine; N-[[4-(1,1-dimethylethyl)phenyl] methyl]-N-methyl-1-naphthalenemethanamine.

The anti-fungal hydroxy pyridines suitable for use can be selected from Hydroxy pyridinessuch as 6-cyclohexyl-1-hydroxy-4-meethyl-2(1H)-pyridone, 2-aminoethanol salt,polymers .

The anti-fungal polymers suitable for use can be selected from Nystatin and [1R(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E, 29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,-39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid; Methyl(3-methylphenyl)-carbamothioic acid O-2-naphthalenylester, (1'S,6'R)-7-chloro-2',-4,6-trimethoxy-6'-methylspiro[benzofuran-2(3H),1'-[2]cyclohexene]-3,4'-dione .

It is surprisingly found by way of the present invention that anti-fungal agents such as α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine-hydrochloride can be effectively solubilized by the use of the selected carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives.

The above pharmaceutical composition of the invention resolves all the existing difficulties in the preparation of anti-fungal compositions through a simple technology, whereby anti-fungal compounds, which are otherwise difficult to solubilize can be selectively solubilized to be easily prepared in various formulations.

This, therefore, unexpectedly provides for the much desired simple and cost-effective pharmaceutical composition for wide range of anti-fungal application.

It is found by way of the present invention that various anti-fungal preparations such as of α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and

N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in the form of injectables, tablets, oral liquids, pessaries, suppositories, gels, lotions, sprays and ear or eye drops could be formulated using 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives as solvents in an appropriate proportions for treating fungal infections found in animals including mammals.

In accordance with another aspect of the present invention there is provided a process for the preparation of the anti-fungal composition of the invention comprising:

providing at least one anti-fungal agent selected from anti –fungal azoles, anti-fungal allylamines, anti-fungal hydroxy pyridines and anti-fungal polymers in a selective carrier media comprising at least one of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives.

In particular, the formulations can be prepared by dissolving at least one of said anti-fungal agents such as atleast one of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol; and N-[(2E)-6,6-Dimethyl-2-hepten-4ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in the selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol or its derivatives.

Alternatively the pharmaceutical composition of the invention in solution form can be added to formulate tablets containing excipients such as starch or lactose or may be directly filled in capsules, alone or with suitable excipient/s, or in the form of drops or suspension containing flavouring or coloring agents or directly for parenteral administration.

Importantly, the pharmaceutical composition of the invention in sterile solution form can be directly administered intramuscularly or intravenously or by diluting it in an infusion.

The invention thus provides a simple method for formulating compositions especially of anti-fungal agent such as α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalene-methanamine hydrochloride in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol

solution to offer a clear transparent solution which is safe and effective for therapeutic applications.

The invention by way of the selective carrier avoids the problems of providing simple and cost-effective anti-fungal formulation which can be administered in saline or glucose infusions or can be administered in the form of syrups or suspension or it can be applied directly to skin or it can be administered orally in the form of tablets for a longer duration till a patient responds to such infection.

The pharmaceutical compositions of the invention is thus a simple, safe and cost effective formulation which can be administered either directly or by modifications therein.

Details of the Invention:

It has thus been possible by way of the present invention to provide compositions comprising of anti-fungals like α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine- hydrochloride in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol as a selected pharmaceutical composition suitable for parenteral, oral and local administration as solutions, tablets, eye and ear drops, lotions, ointments, pastes, dusting powders, gels and sprays. The compositions can also be used for the preparation of nail polishes, suppositories, pessaries, etc.

In accordance with a preferred aspect the process for the preparation of the anti-fungal composition comprise of:

providing of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol as a carrier media followed by stirring, heating and cooling to obtain clear solution.

According to another preferred aspect the process for preparation of the composition comprise of:

providing N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol as a carrier media followed by stirring, heating and cooling to obtain clear solution.

Thus by way of the present invention anti-fungals such as α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalene-methanamine hydrochloride formulation as described above can be directly administered orally or can be easily incorporated in the form of tablets, capsules, oral liquids, injectables or by direct application as gel, cream, lotion, suppositories. The compositions in the desired concentrated solution form, can achieve the therapeutic level of the drug if chosen for such application, as the solvent 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives have good aqueous solubility and are further safe, cost effective and efficacious in terms of drug delivery.

The compositions in solution form, prepared in the solvent, can be readily used as single or multi dose vials for therapeutical applications.

The solution can be used in the injectable form for quick availability of the drugs in the blood, since if a drug is injected intravenously or intramuscularly the drug can by pass the first pass metabolism.

It is found that oral dose of 100 mg - 400 mg of α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol or 250 mg of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride administered therapeutically in the treatment of mycotic infections is effective.

As apparent from the above the selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives can be used for the preparation of various anti-fungal preparations including derivatives of azoles like 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)-D-threo-penitol; (αR,βS)-α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-

yl)methyl)-4-pyrimideethanol; 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile and alike to achieve the same goal of therapeutic application.

The formulation of the present invention offers an advantage of administering the anti-fungal actives in solution either through Intramuscular or Intravenous route or through rectal suppositories Further the formulation of such composition can be used for the treatment of yeast infections in the form of vaginal pessaries.

It is possible by way of the present invention to provide anti-fungal in capsules from in the range of 50 mg/cap – 250mg/cap or as tablet containing 125 - 250 mg. of the drug or can be administered directly as an oral drop without diluting or formulating in the oral syrup form in the concentration of 125mg - 250 mg/5ml with necessary excipeints, or for the local application as 1% (10mg/gm) sprays, lotions, creams, gels, ointments with the necessary excipients. Hence, this concentrated solution following the present invention offers desired varied and effective therapeutic use of the anti-fungal agents not possible under the prevailing state-of-art of anti-fungal formulations and their uses.

The concentrated solution prepared by way of the present invention can be filled directly in the capsules in the concentration range of 50 – 250 mg/cap with or without diluents or can be prepared as tablets in the concentration range of 50 – 125 mg/ml solution with necessary diluents or can be administered Intramuscularly or Intravenously, which can be further diluted with water to achieve the desired concentration required in the treatment of extensive systemic Mycotic infection.

The concentrated solution of the invention can further be administered as drops (50 – 125 mg/ml) directly or as a syrup in the same concentration by adding the necessary diluents. Furthermore, this solution can be used in the preparation of sprays, lotions, gels, creams, ointments & laquers containing 1% - 2.5% of the drug. Suppositories and pessaries of 50 mg-250 mg can be prepared by mixing of the drug with the necessary excipients.

EXAMPLES

This invention is illustrated hereunder in greater detail in relation to the non-limiting examples for the preparation of α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride with 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and medium of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol & water as a selective carrier.

Example I :

α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol clear solution can be obtained as 0.0327 mole of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol, which is taken in a round bottom flask having the facility to stir and to flush nitrogen. 50 ml of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol is added and stirred at 37°C till it dissolves and dilutes to 100 ml, This mixture is then flushed with Nitrogen and filtered aseptically through 0.22μ filter and filled in suitable vials which can be used when preparing infusions, oral dosage forms such as drops or oral liquids by incorporating necessary excipients like diluents/sweetners flavouring agents, stabilizer for oral liquid or by diluting with alcohol & propellent to prepare spray or by filling the liquid in soft gel or hard filled capsules of suitable size or can be used for preparing vaginal pessaries or suppositories, eye drops or ear drops.

Example II :

0.0327 mole of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol is taken in a round bottom flask which has the facilities to stir and flush Nitrogen. 50ml of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol, 0.2115 mmole of αTocopherol acetate is added to the solution with continuous stirring at 40°C for 45 minutes. The mixture is then cooled to room temperature and the resultant solution is made to 100ml. This solution is filtered through 0.22μ filter and fill and sealed in suitable vials under hermatic conditions which can be used for preparing infusion, oral dosage forms such as drops or liquids by incorporating necessary excipients like diluents/sweetners flavouring agents, stabilizer for oral liquid or by diluting with alcohol & propellent to

prepare spray or by filling the liquid in soft gel or hard filled capsule of suitable size or can be used for preparing vaginal pessaries or suppositories, eye drops or ear drops.

Example III :

0.0327 of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol is taken in a 100 ml round bottom flask containing 50 ml of 2,5-di-O-methyl-1,4:3,6-dihydro-D-glucitol which has the facilities to sir and flush Nitrogen. Heat the solution at 40°C for 30 minutes, cool the mixture at 25°C. Add 50 ml injectable grade water along with 0.7 mmole of chlorocresol and the resultant solution is made to 100 ml. The pH of this solution is measured potentiometrically, which is about 6. Then this solution is aseptically filtered through 0.2μ filters and filled in suitable vial. Omitting chlorocresol and by adding necessary diluents the oral dosage forms like oral liquid, gel, cream and spray, ear and eye drops can be prepared.

Example IV :

0.0343 mole of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine is taken in a round bottom flask fitted with 2 necks containing facilities for stirring and for flushing of Nitrogen. 50 ml of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol is added by stirring at 40°C for half an hour. Nitrogen is then flushed into the solution. The resultant solution is cooled to 25°C and made to volume of 100 ml then filtered aseptically through 0.22μ membrane into a vial. This solution can be used as concentrate for making infusion or added as a dispersing agent for the preparation of tablets or is directly filled in soft/hard gelatin capsules or prepared as oral liquid using a suitable sweetening agent, flavouring agent and stabilizer or can be used for preparing pessaries or suppositories or can be used for preparing external applications such as sprays, lotions, lacquers, nail polishes or gels, ointments, creams, ear and eye drops for treating infections caused due to mycoses.

Example V :

0.0343 mole of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine is taken in a 100ml round bottom flask having the facility for stirring and for flushing of Nitrogen. 50ml of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-

glucitol is added and stirred for half an hour at 45°C. 0.236 mmole of α Tocopherol acetate is added while stirring and stirred further for half an hour. The mixture is cooled to room temperature at 25°C and the resultant solution is made to 100 ml, filtered aseptically through 0.22μ membrane and filled in a vial. This solution can be used directly for intramuscular or intravenous use or infusion can be prepared for suitable therapeutic use, or oral formulations like tablets can be prepared by dispersing in suitable diluents or can be directly filled in suitable hard filled or soft gelating capsules or can be used as drops by suitably mixing with a sweetning flavour and stabilizing agent or can be used as lotion for local application or mixed with suitable vehicle to prepare sprays, lacquers, nail polishes, creams, gels, ointments or for the preparation of pessaries, suppositories or ear and eye drops.

Example VI :

0.0343 mole of N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine is taken in 100ml round bottom flask having the facilities for stirring and flushing of nitrogen. 50 ml l of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol is then added. 0.7 mole of chlorocresol is also added with stirring and 50 ml of injectable grade water is further added with continuous stirring. The resultant solution is filtered aseptically through 0.2μ membrane and filled in vials after flushing with nitrogen.

This solution without chlorocresol can be used to prepare oral drops, oral liquid, lotions for local application or can be used for preparing gels, creams or for sprays.

These solutions of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine were subjected to stability studies for the assay as per ICH guidelines and show good stability. Results are illustrated as follows :

PERIODIC STABILITY STUDY DATA

Product : α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol

Storage Condition : At 25° C ± 2°C /60 ± 5% RH

Example - I

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	100.9%	100.7%	100.7%	100.0%	99.9%

Example - II

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	101.0%	100.5%	100.4%	100.0%	99.8%

Example - III

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	101.0%	100.8%	99.88%	99.0%	99.0%

ACCELERATED STABILITY STUDY DATA

Product : α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol

Storage Condition : At 40°C ± 5°C /75 ± 5%RH.

Example - I

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	100.9%	99.8%	99.3%	99.1%

Example - II

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	101.0%	100.8%	99.5%	98.9

Example - III

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	101.0%	99.8%	99.6%	99.3%

PERIODIC STABILITY STUDY DATA

Name of Product : N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine

Storage Condition : **At 25° C ± 2°C /60 ± 5% RH**

Example IV

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	99.8%	**99.55%**	**99.6%**	**99.7%**	**99.2%**

Example V

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	101.3%	**99.98%**	**99.93%**	**99.5%**	**99.5%**

Example VI

Sr. No.	Test	Limit	Initial	3 months	6 months	9 months	12 months
1	Assay	95% - 105%.	100.8%	**100.3%**	**100.1%**	**100.1%**	**99.0%**

ACCELERATED STABILITY STUDY DATA

Name of Product : N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine

Storage Condition : **At 40°C ± 5°C /75 ± 5%RH.**

Example IV

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	99.8%	**99.6%**	**98.8%**	**98.0%**

Example V

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	100.5%	100.05%	98.85%	**98.5%**

Example VI

Sr. No.	Test	Limit	Initial	2 months	4 months	6 months
1	Assay	95% - 105%.	100.8%	99.7%	99.3%	**99.15%**

Thus it can be seen that the prepared concentrated preparations of α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in the concentration of up to 100 mg/ml with or without water and with or without antioxidant is chemically stable. Water up to 50% can be easily mixed during formulation and is tested by stability indicating HPLC method.

TEST OF ANTI-FUNGAL ACTIVITY OF THE FORMULATION OF THE INVENTION:

Invitro evaluation of anti-fungal activity of preparations of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride was performed by determining the Minimum Inhibitory Concentration (MIC) which is the concentration of the test compound in a suitable medium, wherein, the growth of the fungus fails to occur. It is carried out on agar plate method wherein, particular concentration of test compound is incorporated in media containing test organism. Each plate is inoculated for 48 hours at 37°C and these plates are examined for the presence of growth or absence of growth and then the Minimum Inhibitory Concentration is noted.

The species which were tested for Minimum Inhibitory Concentration were for α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol solution and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride solution are as follows :

A

α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol solution	**Observed Minimum Inhibitory Concentration**
Candida albicans	120µg/ml
Candida tropicalis	100µg/ml
Candida krusei	50µg/ml
Cryptococcus neoformans	60µg/ml

B

N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride solution	**Observed Minimum Inhibitory Concentration**
Candida albicans	6.25mcg/ml
Epidermophyton	0.1mcg/ml
Aspergillus Spp.	5 mcg/ml
Trichophyton rubrum	0.05mcg/ml
Sporothrix Schenckii	1mcg/ml
Cryptococcus neoformans	1mcg/ml

The above clearly reveal the suitability of the preparation of the invention as an effective anti-fungal composition in treating various species related fungal infections.

CLAIMS

1. An anti –fungal pharmaceutical composition comprising at least one anti –fungal agent selected from anti –fungal azoles, anti-fungal allylamines, anti-fungal hydroxy pyridines and anti-fungal polymers in a selective carrier media selected from 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives.

2. A pharmaceutical composition as claimed in claim 1 wherein said anti-fungal agent comprise anti-fungal azoles selected from 1-[(2-chlorophenyl)-diphenylmethyl]-1H-imidazole; 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole; 1-[2-[(2-chloro-3-thienyl) methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine; 1-[2-[(4-chlorophenyl)-methoxy]-2-(2,4-dichloro-phenyl)ethyl]-1H-imidazole; rel-1-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-ethylethyl)piperazine; 1-[2-(2,4-dichlorophenyl)-2-[(2,6-dichlorophenyl)methoxy] ethyl]1H-imidazole; (Z)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanoneO-[(2,4-dichlorophenyl) methyl]oxime; 1-([1,1′-biphenyl[-4-yl-phenylmethyl)-1H-imidazole; 1-[2-[(7-chlorobenzo[b]thien-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; 1-[2-[[(4-chlorophenyl)methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole; α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol; 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one; (αR,βS)-α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-4-pyrimideethanol; 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile; 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl] phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)-D-threo-penitol

3. A pharmaceutical composition as claimed in anyone of claims 1 or 2 wherein the said anti-fungal allylamines is selected from N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-

methyl-1-naphthalenemethanamine hydrochloride;(E)-N-methyl-N-(3-phenyl-2-propenyl)-1-naphthalenemethanamine; N-[[4-(1,1-dimethylethyl)phenyl] methyl]-N-methyl-1-naphthalenemethanamine .

4. A pharmaceutical composition as claimed in anyone of claims 1 to 3 wherein said anti-fungal Hydroxy pyridines comprise 6-cyclohexyl-1-hydroxy-4-meethyl-2(1H)-pyridone, 2-aminoethanol salt.

5. A pharmaceutical composition as claimed in anyone of claims 1 to 4 wherein the anti-fungal polymers are selected from Nystatin and 1R(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E, 29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,-39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid; Methyl(3-methylphenyl)-carbamothioic acid O-2-naphthalenylester, (1′S,6′R)-7-chloro-2′,-4,6-trimethoxy-6′-methylspiro[benzofuran-2(3H),1′-[2]cyclohexene]-3,4′-dione.

6. A pharmaceutical composition as claimed in anyone of claims 1 to 5 wherein said anti-fungal agent comprises 0.1% to 10% by wt. of the composition.

7. A pharmaceutical composition as claimed in claim 6 wherein said anti-fungal agent is selected from α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol and N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride present in a concentration range of 0.1% to 10% of the composition.

8. A pharmaceutical composition as claimed in anyone of claims 1 to 5 wherein for paranteral use anti-fungal agent selected from α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol & N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride comprise water from 1% to 50% w/v.

9. A Pharmaceutical composition as claimed in claims 1 to 8 comprising antioxidants selected from Tocopherol derivatives, Ascorbyl palmitate, Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and other antioxidants preferably sodium meta bisulphite.

10. A Pharmaceutical composition as claimed in anyone of claims 1to 9 wherein the antioxidants preferably are selected from the category of Vitamin E in the range of 0.02% to 0.1% w/v.

11. A Pharmaceutical composition as claimed in anyone of claims 1 to 10 comprising composition stabilizers comprising of phenolic derivatives and preferably chlorocresol or metacresol.

12. A Pharmaceutical composition as claimed in anyone of claims 1 to 11 comprising other additives for oral formulations selected from tablet diluents, sweetners, flavouring agents suitable for administration through oral route in the form of liquid or drops or suspensions by filling directly in capsules with or without diluents.

13. A Pharmaceutical composition as claimed in anyone of claims 1 to 12 in the form of lotions, liquids, creams, talcum powders ointments, sprays, eye drops, ear drops with or without propellant or as lacquers as a nail polish for topical application, eye and ear drops and for the preparation of pessaries and suppositories.

14. A Pharmaceutical composition as claimed in anyone of claims 1 to 13 comprising said α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives in the concentration range of 50mg/ml to 100mg/ml preferably, 75mg/ml to 100mg/ml.

15. A Pharmaceutical composition as claimed in anyone of claims 1 to 13 comprising said N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives in the concentration range of 50mg/ml to 125 mg/ml preferably 50mg/ml to 100mg/ml.

16. A Pharmaceutical composition as claimed in anyone of claims 1 to 13 wherein it is in tablet form containing 50mg to 250 mg of the active anti-fungal.

17. A process for the preparation of the anti-fungal composition as claimed in claim 1 comprising:
providing at least one anti-fungal agent selected from anti –fungal azoles, anti-fungal allylamines, anti-fungal hydroxy pyridines and anti-fungal polymers in a selective carrier media comprising at least one of 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol and its derivatives.

18. A process for the preparation of anti-fungal composition as claimed in claim 17 comprising dissolving at least one of said anti-fungal agents preferably atleast one of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol; and N-[(2E)-6,6-Dimethyl-2-hepten-4ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in the said selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol or its derivatives.

19. A process for the preparation of anti-fungal composition as claimed in anyone of claims 17 or 18 wherein to formulate tablets said solution of anti-fungal agent and selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol or its derivatives is added to excipients preferably starch or lactose .

20. A process for the preparation of anti-fungal composition as claimed in anyone of claims 17 or 18 wherein to obtain capsules said solution of anti-fungal agent and selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol or its derivatives is directly filled in capsules, alone or with suitable excipient/s.

21. A process for the preparation of anti-fungal composition as claimed in anyone of claims 17 or 18wherein to formulate drops or suspensions said solution of anti-fungal agent and selective carrier 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol or its derivatives is combined with flavouring or coloring agents .

22. A process for the preparation of the anti-fungal composition as claimed in anyone of claims 17 to 21 comprising
providing of α-(2,4-Difluorophenyl)- α-(1H-1,2,4-triazole-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol as a carrier media followed by stirring, heating and cooling to obtain clear solution.

23. A process for the preparation of the anti-fungal composition as claimed in anyone of claims 17 to 22 comprising
providing N-[(2E)-6,6-Dimethyl-2-hepten-4-ynyl]-N-methyl-1-naphthalenemethanamine hydrochloride in 2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol as a carrier media followed by stirring, heating and cooling to obtain clear solution.

24. Use of pharmaceutical composition as claimed in any of the above claims from 1 - 16 in the form of injection ,oral or for topical application as anti-fungal preparation.

25. Method of treatment of various fungal infections including resistant strains of mycosis comprising applying/administering the anti-fungal composition as claimed in any of the above claims from 1 - 16 .

26. An anti-fungal pharmaceutical preparation and its method of manufacture substantially as herein described and illustrated with reference to the illustrative examples.