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Research Article

Nano formulation of Itraconazole And Mometasone For The Treatment Of Topical Fungal Infection

***[1]Saumya Srivastava, [1]Manoj Kumar Mishra, [1]Nimesh Kumar Dubey**

[1]Department of Pharmaceutics, Shambhunath Institute of Pharmacy,
Jhalwa-211012, Prayagraj, Uttar Pradesh, India.

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ABSTRACT

The present study is aimed to formulate and evaluate the nanoformulation of Itraconazole and Mometasone for treatment of topical fungal infection. Antifungal drug is often used for the treatment of acute and chronic fungal infection. In the present study the main focus was on the pathology, pathogenesis, and consequently topical treatment of candidiasis. Nano-formulation of ointment containing Itraconazole and Mometasone has been prepared from the polymers like polyethylene glycol-4000, polyethylene glycol 400, sodium lauryl sulphate, glycerin and nanocrystals of itraconazole and mometasone. The nano-formulation of Itraconazole and Mometasone was formulated by modified technique and characterized for different parameters. Itraconazole and Mometasone ointment nano- formulations also showed the maximum release of the drug. X-ray powder diffractometry and scanning electron microscopy showed the formulated nano-formulation was in crystalline shape. The formulation was developed and further evaluated by instrumental techniques such as UV spectroscopy. The stability study shows that the formulation is stable for a long duration of time. The result shows that formulation is having better stability, good spreadability and better compatibility. These results indicated that decided aim of work to improving Pharmacokinetic profile of drug has been improved by the formulation of nano-formulation.

In summary, the nanoformulation of Itraconazole and Mometasone ointment drug delivery systems has two main advantages i.e. they are topical preparation as well as nano sized. It can be postulated that nanoformulation may be a best approach to treat the fungal skin diseases.

Corresponding Author: Saumya Srivastava, Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj-211012, Uttar Pradesh, India

INTRODUCTION:

Fugal infection mainly cause by fungal spore. It can be treated with antifungal agents. Itraconazole and mometasone are used for treating that type of topical fungal infection.

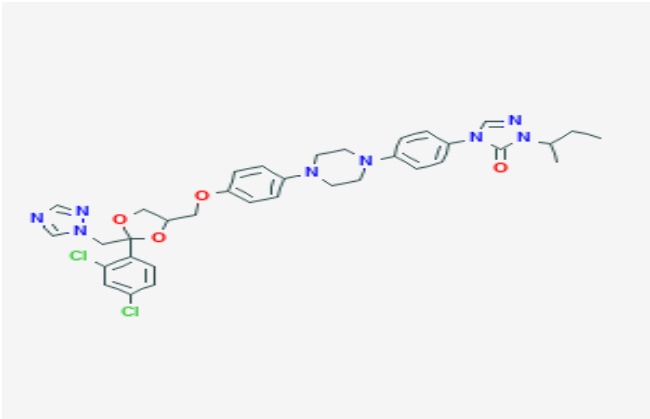
There are two ways in which fungi can grow:

1- Yeast which is fond in single round cell form
2- Molds formed from many cell, these cells are long, thin thread known as hyphae.

There are some fungi which exist in both form during their life cycle. Soil and decaying plant material are the most favorable place for fungi. Some fungi grow in bread molds mushrooms which can be seen without microscope. On human being fungi affects skin hairs and nails. Dermatophytes yeast and mould are main group of fungi which cause superficial infection.

Structure of drugs which are used in this formulation:

Itraconazole:



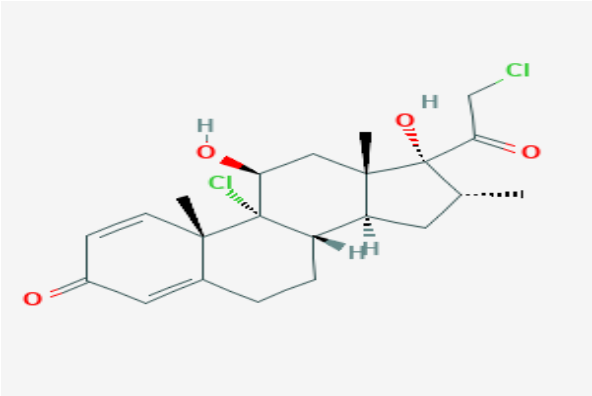
(Fig. 1: Chemical structure of Itraconazole)

Itraconazole is (±)-1-[(*RS*)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*R*,4*S*)-*rel*-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one in IUPAC and having formula $C_{35}H_{38}Cl_2N_8O_4$ and its molecular weight is 705.64 g·mol$^{-1.}$

It comes under antifungal drugs and dosage as recommended 100 mg BD through oral, local or if required through IV. It is not soluble in water but in acidic solution itraconazole is soluble. Melting point of the drug is 166 °C. Bioavailability of Itraconazole is 56% and it metabolized in liver excreted from renal and feacal. It bind with protein 99.8%. Itraconazole is an antifungal moiety which comes under triazole category and it shows antimycotic action. It can be delivered either systemically or topically. Itraconazole decreases synthesis of ergosterol by inhibiting fungal enzymes cytochrome p450. Chronic and acute both fungal infection can be treated by this agent as it is safe for prolonged uses.

Mometasone:

Mometasone is (9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-17-yl furan-2-carboxylate in IUPAC and having formula $C_{22}H_{28}Cl_2O_4$ its molecular weight is 427.361g/mol.



(Fig. 2:Chemical structure of Mometasone)

Mometasone comes under corticosteroid and glucocorticoid drugs. And can be used to treat allergies inflammations and dermatological infections. It can be given topically or through nasal inhalation.

Mometasone is not soluble in water but soluble in acetone chloroform and tetrahydrofuran. It melts at 220 °C and having protein binding 98 %.

Mometasone is also used as antifungal drug as it reduces skin inflammation. It is also used as vasoconstrictor and antipruritic drug. Mometasone is widely used in asthma and it can be delivered topically or systemically. It has lack of active metabolites and shows primarily local effects. It is mainly corticosteroids or steroidal glucocorticoid which is

synthetic and having low potency. Mometasone furoate is prodrug for mometasone. Mometasone is agonist of the mineralocorticoid so it is used as progestogenic drug and shows potent effect.

MATERIAL AND METHODS:

Chemicals and reagents:

Methanol H.P.L.C. grade
Water H.P.L.C. grade
Polyethylene glycol- 400
Polyethylene glycol- 4000
Glycerin
Sodium Lauryl Sulphate
Candida *albicans* fungal stain

Instrumentation:

Electronic weighing balance
Ultrasonic bath sonicator
Magnetic stirrer
Double beam Ultraviolet spectrophotometer
Centrifuge
Brookfield Viscometer
pH meter
FTIR
SEM
X-ray Diffractometer

Formulation method of Itraconazole Mometasone Nanoparticles:

Solvent diffusion method was used for preparation of formulation. 44.2 mg of Itraconazole and Mometasone were measured through weighing balance and taken into a 20 ml volumetric flask.
Little amount of water was added to this and sonicate for few minutes. After that volume make up to 20 ml and sonicate for 40 minute.
This solution was stir at low speed through magnetic stirrer for 10 hrs after that it get converted into nano from.
Nanoparticle were separated by centrifuge it at 15000 rpm this process was done for 30 minute.
Separated particles were dried into hot air oven until it dried.
Dried nanoparticles were collected into eppendorf.

Preparation of topical nanoformulation ointment:

Ointment base was used for Itraconazole Mometasone Nanoformulation. This base was prepared by dissolving polyethylene glycol 400 into polyethylene glycol 4000 on hot plate and adding pinch of soldium lauryl sulphate and little bit of glycerin. Let it cool and when it reaches to room temperature it gets ointment like texture.
Nanoparticles of Itraconazole and Mometasone were added to the ointment base by geometrical method by continuous folding the drug and base on the slab. Now it stored into air tight container. Six different composition of formulation were prepared for evaluating best one. Quantities of different compositions are as follows:

Table 1: Formulation development for nanoformulation ointment

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Itraconazole (mg)	1.4	1.2	1.5	1.1	1.3	1.2
2	Mometasone (mg)	1.2	1.6	1.3	1.2	1.1	1.3
3	Polyethylene Glycol- 400 (ml)	50	40	60	55	45	35
4	Polyethylene Glycol-4000 (gm)	50.4	60.6	40.7	45.1	55.4	65.4
5	Glycerine (ml)	1.5	1.5	1.5	1.5	1.5	1.5
6	Sodium lauryl sulphate (mg)	0.2	0.15	0.15	0.15	0.1	0.15

Preformulation Studies

Preformulation studies carried out for the raw drug to identify them and to know characteristics of drug. In this process various chemical tests were performed like solubility test, pH, Melting point, tests of physical characteristics like appearance, odor, taste and test for knowing its potency.

RESULT:

Identification of Drug

Appearance : Itraconazole and Mometasone were tested for their physical parameters it checked with naked eye for its appearance and both are **white powder** and it complies with the guideline

Odor: Itraconazole and Mometasone was **odorless**

Chemical Tests: Chemical test were performed for identification of Itraconazole and Mometasone and found **Positive**.

Melting Point: Melting apparatus was used for testing melting point and it was **167** degree Celsius for Itraconazole and 223 degree Celsius for Mometasone.

Solubility of Drug

Different solvent were used for the analysis solubility. Itraconazole and Mometasone were tested form its solubility by dissolving these drugs into different solvent and it found that:

Itraconazole is **soluble** in methanol and it is **insoluble** in water and 0.1HCL

Mometasone is **soluble** in methanol and dichlormethane and **insoluble** in water.

Table 2: Evaluation results of various nanoformulations

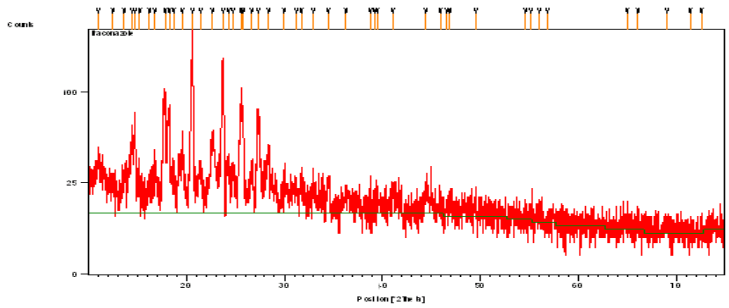
Formulation code	pH	Extrudability	Spreadability	Viscosity
F1	7.04	Average	1.68	918
F2	6.24	Excellent	1.96	990
F3	7.09	Good	1.18	160
F4	7.4	Excellent	1.49	447
F5	6.95	Good	1.98	847
F6	6.81	Average	1.63	1040

Test for activity of Candida *albicans*:

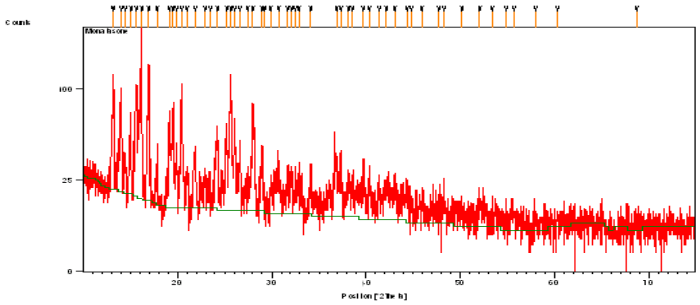
Antifungal activity of the formulation was determined by cup plate method. In this test Sabouraud dextrose agar used as a culture media for culturing candida albicans. Study started on this by placing little amount of our nanoformulation and kept in incubator for 18 hour. After that zone of inhibition was noted and it was 4mm due to which we can assume that nanoformulation of Itraconazole and Mometasone is capable for inhibiting the fungal growth and cause cell death of fungi by inhibiting synthesis of ergosterol in fungal cell.

X-ray powder diffraction study (XRPD):

Nanoparticale were analyzed for their particle size by X-Ray Powder Diffractometer and following graph obtained from analysis:



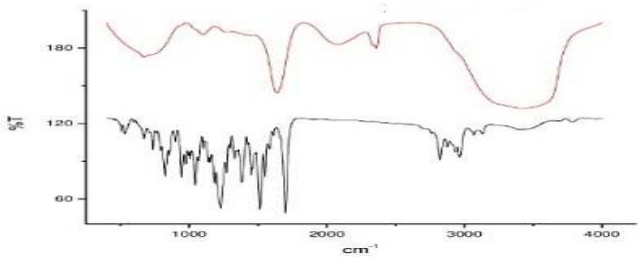
(Fig. 3: XRD of Itraconazole)



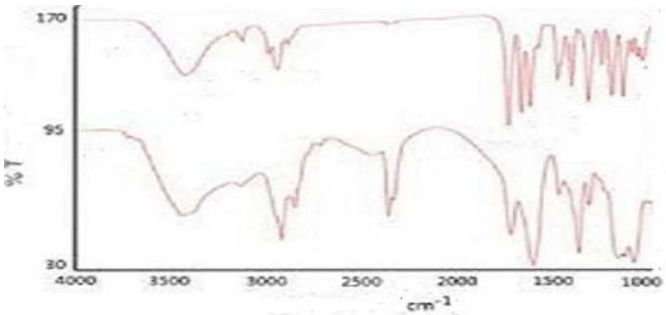
(Fig. 4: XRD of Mometasone)

Infra-red spectroscopy:

IR spectrophotometer was used for identification of functional groups and spectra are as follows:



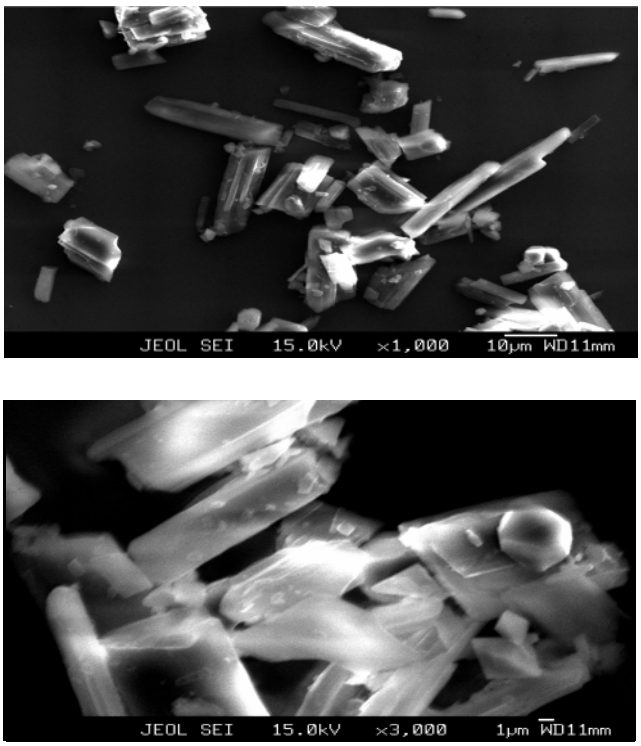
(Fig. 5: FTIR of Itraconazole nanoformulation and Itraconazole drug)



(Fig. 6: FTIR of Mometasone nanoformulation and Mometasone drug)

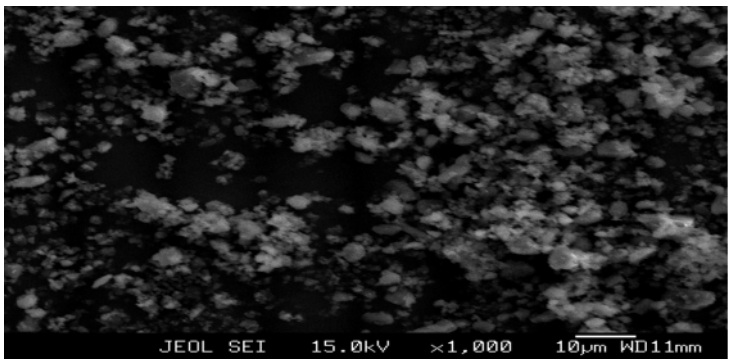
Scanning Electron Microscopy:
Itraconazole and Mometasone nanoparticle tested for their morphology through scanning electron microscope and following reports were obtained:

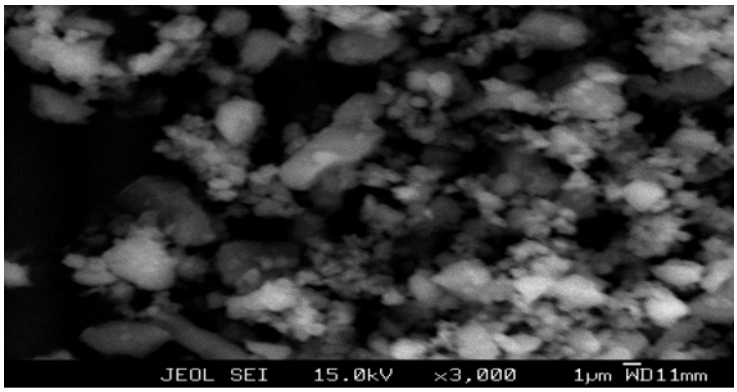
SEM Itraconazole:



(Fig. 7: SEM Report of Itraconazole crystals)

SEM Mometasone:





(Fig. 8: SEM report of Mometasone crystals)

Entrapment efficiency:

65.95 %	Formulation-1
94.59 %	Formulation-2
81.86 %	Formulation-3
89.49 %	Formulation-4
85.45 %	Formulation-5
91.63%	Formulation-6

Stability testing:

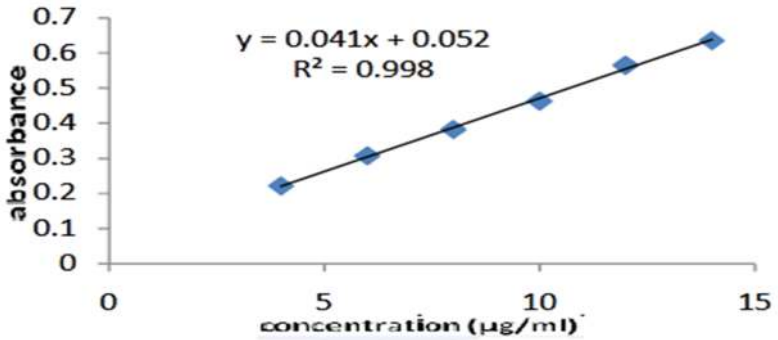
Formulation 2 was carried out for stability testing as it was optimized batch and. It studied at three month real time study at 25 degree Celsius and 60 % relative humidity in a stability chamber. After that formulation were found in same condition and complies the guideline.

U.V. Analysis:

Drugs were scanned between max 240-400 nm and comparison was done from standard spectra of drug. At λ 262 & 248 wavelength Itraconazole and Mometasone furoate were found respectively. In this analysis assay of drug was obtained 99%.

U.V. Analysis of Itraconazole: Methanol was used for preparing dilution of Itraconazole and standard curve was taken on UV spectrophotometer.

The spectra were observed at λmax 262 nm. And the regression value was 0.998

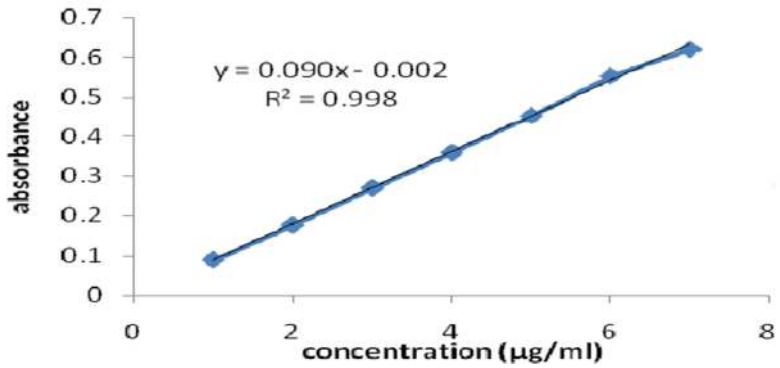


(Fig. 9:Itraconazole UV graph)

UV Analysis of Mometasone:

Methanol was used for preparing dilution of Mometasone and standard curve was taken on UV spectrophotometer.

The spectra were observed at λmax 248 nm. And the regression value was 0.998.



(Fig. 9: Mometasone UV graph)

DISCUSSION:

Itraconazole and Mometasone furoate was formulated in nanoformulation topical ointment which can be more effective for cure of topical fungal infection. As it had poor solubility in water it cannot be good in orally administered dosage form and in case of chronic fungal infection if it is taken orally there is chance of adverse effect. In this formulation nanoparticles prepared from solvent diffusion method. Base was prepared from polymer like polyethyleneglycol400 and polyethylene glycol 4000 and glycerine, sodium lauryl sulphate then nanoparticles were incorporated into ointment base through geometrical method. This topical nanoformulation was hypothesized to treat fungal infection.

CONCLUSION:

Nanoformulation of itraconazole and mometasone was prepared in ointment dosage form, for treating topical fungal infections. Solvent diffusion method was used to formulate this ointment. Raw drug was converted into nanoparticles and then incorporated into ointment base. After that it was evaluated for various factors for quality testing of preparation. In UV analysis of drug Assay was 99%. FTIR were performed for functional group identification. Powder XRD was done. Scanning Electron Microscopy was done for nanoparticle size determination. Various physicochemical tests were performed for quality test of preparation and it was found that all tests comply the standard. Nanoformulation prepared so that it can show better antifungal activity at the site of application and recover the local site which is infected by fungal spore.

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