Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **44** Special Issue **-2 Year 2023** Page **2637:2662***

"Research on the "Engineering of Nano-gel for delivery of Mometasone and Itraconazole on Scalp and Beard for the Treatment of Fungal Infection"

Saumya Srivastava 1*, Dr. Shikhar Verma[1]

1. Maharishi School of Pharmaceutical Sciences, Maharishi University of Information Technology, IIM Road, Lucknow

First Author's E-mail: saumyasrivastava25@gmail.com
Corresponding Author's E-mail: vermashikhar001@gmail.com

Article History
Received: 08July2023
Revised: 29 Aug 2023
Accepted: 02 Oct 2023

ABSTRACT:

Background- Scalp and beard fungal infection often treated with conventional dosage form like cream, gel, emul-gel, which causes various side effects, to overcome such problems this research was conducted to develop Itraconazole and Mometsone Anti-fungal Nano-Hydro- Gel that is effective in the treatment of fungal infections of the scalp and beard. Itraconazole belongs to Azole group, which inhibit Lanosterol 14 alfa demethylase, the enzyme that converts lanosterol to ergosterol. Ergosterol is a component of yeast and fungal membranes. Nano-formulation penetrates deeper into the skin. The gel formula retains its therapeutic effect as well as the soothing effect on the hair follicles for long time. Pre-formulation studies of Itraconazole and Mometasone particles were done, and then both the API particles were converted into nano- particles through solvent diffusion method. SEM, P-XRD, IR tests were performed for characterization of Nano-Particles. Nano- Hydrogel base, prepare by using Carbopol-940, Carbopol-934, Triethanolamine and Distilled Water

and engineering done by adding drug. When both Carbopol grades (934 and 940) are used together in the formulation of gel, the drug will release over a longer period of time with a smaller dose and less chance of any dose-dependent harm.Various composition were engineered an evaluated for selection of model formulation.

Result- Evaluated for these parameters: Physical appearance, pH, estimation of practical yield, homogeneity, drug content uniformity, spreadability, viscosity, Statistical analysis of experimental data by ANOVA using Excel, In-vitro-drug release study, release kinetic study, Particle size analysis, (SEM), FT-IR studies. In-Vitro Anti-fungal activity tested by using Nano-gel Franz diffusion cell (Make-Orchid scientific). Amount of drug released was determined using UV- spectrophotometer at 222 nm.

Conclusion- Fungal infection is most common skin condition occurs on the scalp and chin. Under these skin conditions, the hair follicles become inflamed and the affected area becomes itchy, flaky or scaly, causing redness, swelling and irritation. So this research was done with focus for pathology, pathogenesis consequently treatment of scalp and beard fungal infection.

Keywords: Nanogel; Antifungal; Scalp and Beard; Mometasone; Itraconazole.

BACKGROUND:

Fungal infection on scalp and beard:

A fungus, such as Tinea barbe, Tinea capitis, seborrheic dermatitis, folliculitis, Candida albicans, Candida thrives, or Pseudofolliculitis barbe, can cause fungal infection of the scalp and chin. On the chin and scalp, it is the most typical skin problem. These skin diseases result in redness, swelling(1), and irritation as the hair follicles become irritated and the affected area becomes itchy, flaky, or scaly. One of the most prevalent fungal infections of the scalp is psoriasis. The

tinea infection often known as ring worm affects the beard area and causes a pattern that resembles a ring.

Numerous factors might lead to a fungus infection on the scalp and hairy chin. Fungi can develop in warm, humid environments. Fungal infection on scalp and chin must be treated on time if remain untreated then it may cause serious health problems by affecting some organ like eye, mouth, digestive system, blood stream, bone and other internal organ.(2)Fungal infections can also be brought by certain medical conditions, an improper diet, stress, some medications, minor cuts, and harsh chemicals.

Risk factor:

One risk factor is that these fungi infections can weaken the immune system and lead to diabetes, hypothyroidism, inflammatory diseases, and other illnesses.

Drug Profile:

Mometasone:

Mometasone furoate is a topical glucocorticoid that has anti-inflammatory, anti-puritic, and vasoconstrictive characteristics. It works by attaching to the glucocorticoid receptor.(3)

Drugs utilized in this formulation have the following chemical composition:

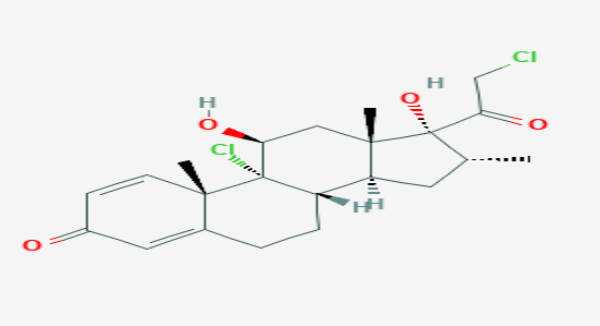


Figure 1- Chemical Structure of Mometasone

Itraconazole: It is an antifungal drug belonging to the triazole class. It works by preventing the cytochrome P-450-dependent enzymes from destroying the synthesis of ergosterol. The presence of ergosterol in fungi's cell membranes is crucial for the fungi's metamorphosis from yeast to mycelial form. Triglyceride or phospholipid biosynthesis is affected by itraconazole.

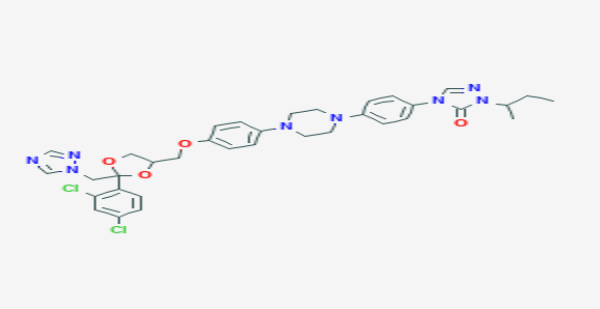


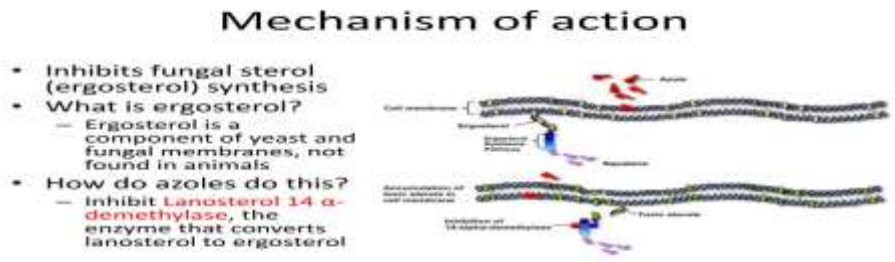
Figure 2: Chemical Structure of Itraconazole

Antifungal Medications: Medication such Terbinafine, Itraconazole, Griseofulvin, Fluconazole, and Ketoconazole are currently available as therapies. Infections of the skin treated with antifungal medication for nails, scalp, and beard. These are treated by using a variety of oral and topical dose forms, including pills, capsules, creams, ointments, lotions, and gels.

Advantage of Nanogel of Mometasone and Itraconazole in beard and scalp fungal treatment:

Mometasone furoate has anti-inflammatory activity and is used in the treatment of various types of skin diseases like psoriasis. It is also a potent drug, so it gives long-lasting action with increased efficacy, which is an advantage of the nanogel of Mometasone and Itraconazole. Itraconazole, a broad-spectrum antifungal medication, is an additional medication included in this formulation. If itraconazole is used topically, patients tolerate it well. However, when itraconazole is used as a traditional oral dosage form, there are more issues and side effects.(4)(5)

Nanotechnological product: Because of its great permeability and durability and its small particle size (20–200 nm), nanogel is created. Due to its strong penetration power, nano-gel has the properties of increased bioavailability, biodegradability, and can diffuse easily. Since nanogel has a hydrophilic nature and can stick to hairy areas for a longer period, it can used to treat fungal infections of the scalp and beard. This formulation will improve the absorption of mometasone and itraconazole through the affected area, leading to improved therapeutic outcomes for a longer period with a calming effect and less greasiness. (6)(7)



METHODS:

Instruments and materials used to make Nano-gel:

Reagents and Chemicals-

Water and Methanol are both of HPLC grade.

Methyl cellulose, Sodium hydroxide, Propyl paraben, Methyl paraben, Carbopol 940, Carbopol 934, Itraconazol, Sodium Lauryl Sulphate, and Candida albicans stain.

Equipment for preparation

Double beam- ultrasonic bath sonicator, magnetic stirrer, electronic weighing balance Centrifuge, Brookfield Viscometer, UV spectrophotometer, pH meter.

Formulation Development Process:

1. Itraconazole nanoparticle formulation: The solvent diffusion method used to create the formulation. Itraconazole weighed using a digital balance and then measured into a 20 ml volumetric flask. The medication mixture is then mixed with a tiny amount of water before being sonicated in a bath sonicator for a few minutes. After this final volume has been raised to the necessary level, sonicate once more on the bath sonicator for about 40 minutes. The solution is then continued stirred using a magnetic stirrer in the following step. To create the nanoparticles, the solution is swirled slowly for ten hours. The procedure produces nanoparticles, which are subsequently centrifuged for 30 minutes on a 15000 Rotation per minute. The liquid component is then separated from the separated particles in the centrifuge tubes, and they are then dried in the hot air oven. They remain in the oven until all moisture has been removed. The dried particles are kept in Eppendorf after they have been acquired.(8)(9)(10)

2. Formation of Mometasone nano-particles: Mometasone Nano-particles were also created using the solvent diffusion method, which involved weighing out the drug and placing it in a 20 ml volumetric flask with a small amount of water. The drug mixture was then sonicated in an

ultrasonic bath sonicator for a few minutes. After this final volume has been raised to the necessary level, sonicate once more on the bath sonicator for about 40 minutes. The solution is then continued stirred using a magnetic stirrer in the following step. To create the nanoparticles, the solution is swirled slowly for ten hours. The resultant nanoparticles are then centrifuged at a speed of 15,000 rpm for 30 minutes. The liquid component is then separated from the separated particles in the centrifuge tubes, and they are then dried in the hot air oven. They remain in the oven until all moisture has been removed. The dried particles are kept in Eppendorf after they have been acquired.(11)(12)(13)

3. The creation of carbopol gels with various carbopol concentrations for the nano-gel of itraconazole and mometasone nanoparticles: The amounts of Carbapol 940 and Cabopol 934 were measured, and both substances dissolved in distilled water. In 100 ml of water, carbopol 940 and carbopol 934 of different compositions were added. When both Carbopol grades (934 and 940) are used together in the formulation of gel, the drug will release over a longer period of time with a smaller dose and less chance of any dose-dependent harm. The formulation was mixed in a (14)magnetic stirrer running at 500 revolutions per minute, which was then left in situ for 24 hours so that the carbopol could soak up the water. Itraconazole and mometasone separately dissolved in a tiny amount of ethanol and then thoroughly dissolved in a solution of Carbopol with moderate stirring. To ensure that the gel was properly mixed and homogenous, 2-3 drops of triethenolamine and 10% NaOH were added.(12)(13)(15)(16)

Table 1 - Amount of Ingredients taken for formulation development

S.No.	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
1	Itraconazole (mg)	1.01	1.05	1.12	1.08	1.05	1.04	1.02	1.11	1.06	1.14	1.12
2	Mometasone (mg)	1.02	1.06	1.11	1.02	1.08	1.12	1.04	1.06	1.13	1.17	1.05
3	Carbopol 934 (mg)	100	_	80	50	20	80	50	20	80	50	20
4	Carbopol 940 (mg)	_	100	80	80	80	50	50	50	20	20	20
5	water (ml)	100	100	100	100	100	100	100	100	100	100	100

6	Ethanol	3	3	3	3	3	3	3	3	3	3	3
7	Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Drug Pre-formulation Studies: The term "formulation" refers to the process of inserting a molecule into a chemical system such that it has the solubility, stability, and deliverability necessary to be utilized as a medicine or vaccine. "Pre-formulation" refers to the preliminary examination of a macromolecular system before the formulation is created. (17)(18)

Drug Identification

The physical characteristics of the drug sample were examined, and all parameters matched those that had been officially reported. Every identification test was successful. The substance looked like white powder.(19)(20)(21)

Melting level

Itraconazole's melting point was determined to be 166 °C, while Mometasone's was discovered to be 220 °C.

Table 2 - Preformulation parameters for Itraconazole

S.No.	Parameters	Observation
1	Appearance	white powder
2	Odor	Odorless
3	Chemical test	Positive
4	Melting point	166 °C

Table 3 - Preformulation parameters for Mometasone

S.No.	Parameters	Observation
1	Appearance	white powder
2	Odor	Odorless
3	Chemical test	Positive
4	Melting point	220 °C

Solubility of Drug: It was discovered that both powder drugs were only partially soluble in water after solubility testing.

Table 4- Solubility of drug in different medium

S.No.	Media	Inference
1	Purified water	Insoluble
2	Methanol	Soluble
3	0.1 HCL	Insoluble
4	PBS pH 6.8	Insoluble
5	PBS pH 7.4	Insoluble

Table 5- pH of formulations

Formulation	Ph
F1	6.72
F2	6.98
F3	7.04
F4	7.15
F5	6.91
F6	6.82
F7	6.59

Table No 6- Viscosity of formulations

Formulations	Viscosity (cp)
F1	918.34
F2	220.20

F3	165.90
F4	447.76
F5	847.40
F6	1040.23

Table No 7- Formulations Spreadibility:

Formulations	**Spreadability R1**	**Spreadability R2**
F1	1.00	0.98
F2	1.32	1.21
F3	2.20	2.31
F4	1.92	2.10
F5	1.11	1.02
F6	0.95	0.91
F7	1.28	0.96

Table No 8- Extrudability of formulations:

Formulations	**Extrudability**
F1	+
F2	+++
F3	++
F4	+++
F5	+++
F6	+
F7	+++

Excellent (+++), Good (++), Average (+), Poor (-)

In-Vitro antifungal activity: Candida *albicans* antifungal activity of F2 was studied by using Cup –Plate method. This antifungal experiment was conducted using the Sabouraud dextrose agar medium. After an 18-hour incubation period, a zone of inhibition was discovered. An obstructed zone measuring 4 mm was found. It proves that the topical Nano formulation ointment containing Itraconazole and Mometasone went into fungal cells where it may have caused cell death by preventing the synthesis of ergo sterol in the cell wall.(22)(23)

X-Ray Powder Diffraction study

Itraconazole and Mometasone nanoparticles were analyzed for XPRD using an X-ray diffractometer. The images below display the outcomes.

.

Figure 3 (Itraconazole)

Graph (A)

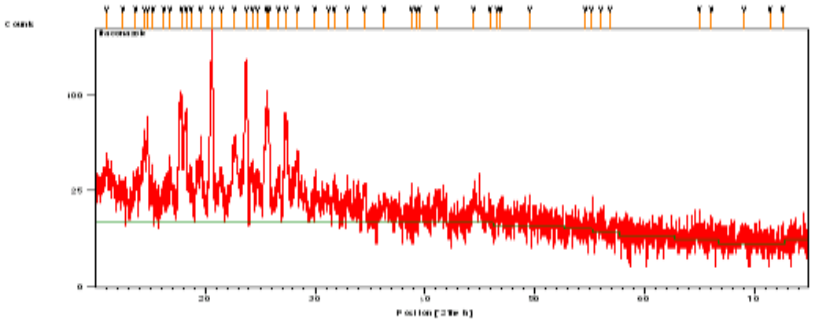
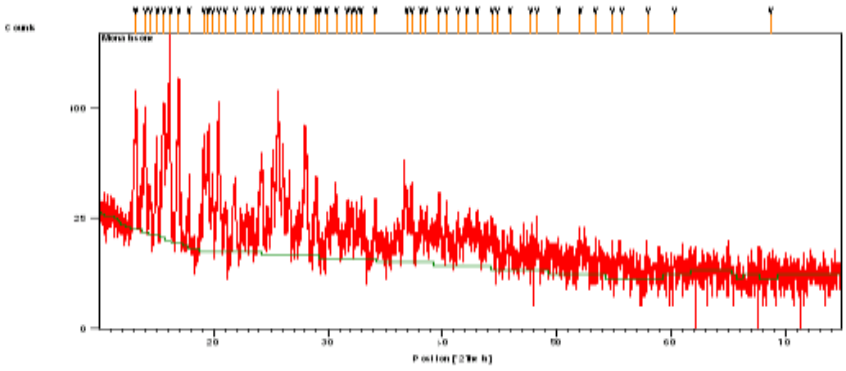


Figure 4 (Mometasone)

Graph (B)



X-ray diffraction of (A) Itraconazole and (B) Mometasone

Scanning Electron Microscopy (SEM):

The following photographs show the examination of the morphology of Itraconazole and Mometasone nanoparticles using scanning electron microscopy.

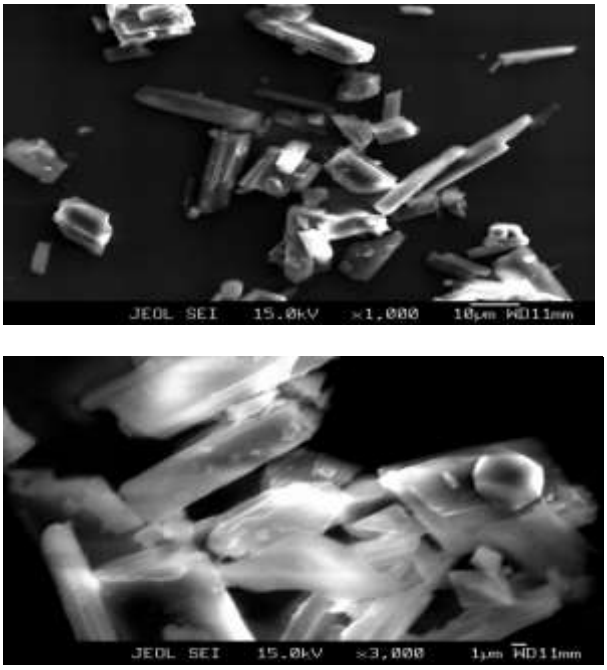


Figure 5- SEM Report Image of itraconazole nanoparticle

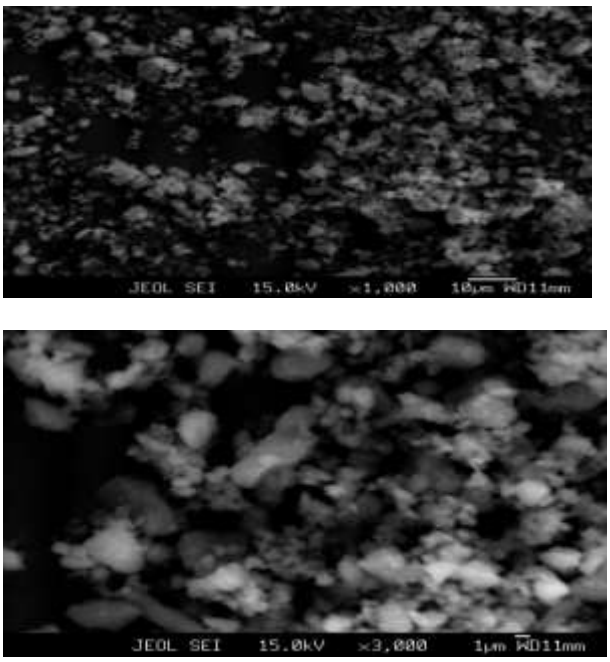


Figure 6- SEM Report- Image of mometasone

Table No 9- Entrapment efficiency:

Formulations	Entrapment efficiency (%)
F1	68.34 ± 2.01
F2	85.84 ± 1.21
F3	82.69 ± 1.32
F4	80.35 ± 1.84
F5	75.10 ± 1.29
F6	73.72 ± 2.60

Stability studies: Examining several parameters during a three-month stability investigation of an optimized batch of topical Nano formulation (F2) at 25± 0.5 °C and 60± 0.5% RH in a stability chamber. These findings showed that the topical Nano formulation was stable and followed ICH guidelines.(24)

U.V. Spectroscopy of Drug: The UV spectrophotometer was used to scan the drug sample in the max 240-500 nm range. The drug's UV spectra were run and contrasted with those of other drugs. The highest absorption of itraconazole and mometasone furoate, which fully complies with pharmacopoeia specification, were discovered at 262 & 248 wave-length. The drug sample was nearly 99% pure according to the official analysis.(25)(26)

Analytical Method Development- Standard Curve of Itraconazole in Methanol: Itraconazole dilution was made in methanol, and a standard curve reading was noticed by using a UV spectrophotometer at a maximum wavelength of 262 nm. Regression values R2 = 0.998 result in satisfactory linearity and compliance with Beer's-Lambert law at a concentration of 100 g/ml.(27)

Table 10-Absorbance reading of Itraconazole in methanol at λ max 262 nm

Concentration (µg/ml)	Absorbance (nm)
4	0.211
6	0.302
8	0.389

10	0.461
12	0.560
14	0.033

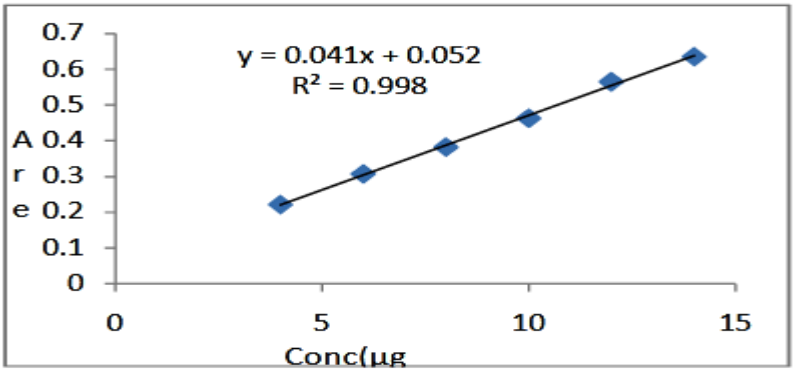


Figure 7- Itraconazole calibration curve using a basic UV spectroscope

Mometasone Standard Curve in Methanol: A UV spectrophotometer with a maximum wavelength of 248 nm was used to produce the mometasone standard curve in methanol. In a concentration of 100 g/ml, the regression value R2 = 0.998 results in good linearity and complies with Beer's-Lambert law.

Table 11-Absorbance reading of Mometasone Furoate in methanol at λ max 248 nm

Concentration (µg/ml)	**Absorbance (nm)**
1	0.088
2	0.175
3	0.269
4	0.358
5	0.452
6	0.553
7	0.620

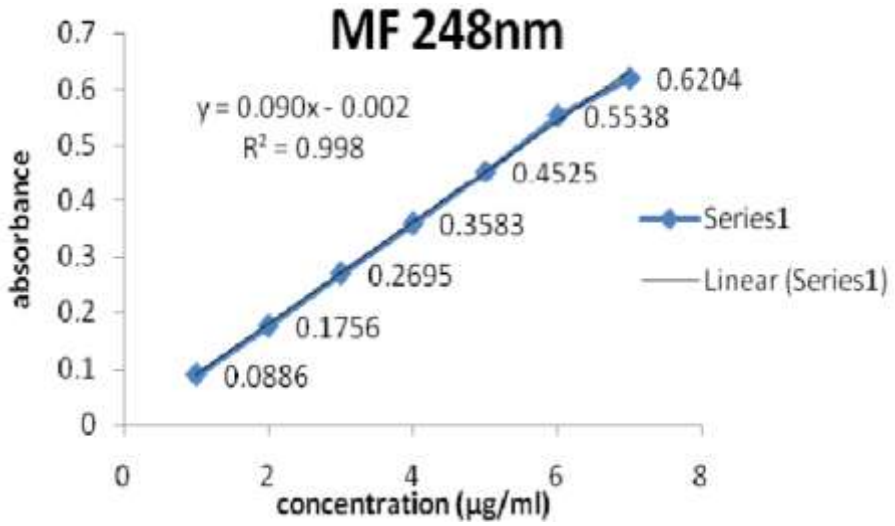


Figure 8: Calibration curve of Mometasone by simple UV spectroscope

Analyzing Nano gel: The features of the Nano gel formulation were assessed, and it was discovered to have good consistency, transparency, and flow characteristics along with evenly distributed particles in the polymer. (28)

Rheology: To ascertain the rheology, the Brookfield viscometer was employed for the Mometasone and Itraconazole Nano gels. Each formulation of the drug's nano-gel was tested for rheological behavior. The rheological behavior of the formulations is directly correlated with their spreadability and contact time. The effect of different gelatin percentages was evaluated using the nanogel's viscosity profile. (29)The nanogel had viscosities of 0.12, 1.16, and 13.43 cp and contained 0.5%, 1.0%, and 1.5% w/v gelatin, respectively. The particles of the Itraconazole & Mometasone-loaded nanogel were 210–252 nm in size. The increasing cross-linking of the gelatin nanogel's polymeric network was the reason for its growing size.(30) The link between sheer stress and the nanogel's shear rate is depicted in Figure 1 in a figure, which also illustrates the behavior of the thixotropic pseudo plastic system. (31)Shear stress increased with yield value as the nanogel's shear rate raised (up curve), showing its pseudo plastic behavior.

Additionally, the thixotropic properties of the material were revealed by the proportional decrease in shear stress as the nano- gel's shear rate was decreased (up curve).(32)

Characterization of nanogel:

Itraconazole and Mometasone nanogel's rheology was evaluated using a Brookfield V 32 rheometer. Three readings were taken at 25ºC.

Viscosity:

Itraconazole and mometasone-loaded nanogel's viscoelasticity was measured using a Brookfield Rheocalc V 32 rheometer. The information needed for the nanogel investigation was produced using Rheocalc. In nanogel, shear rate was investigated at orders from 0 to 50 D [1/s]. Each reading was made three times at a temperature of 25 0C.

HPLC evaluation: For the nanogel experiment, a reverse phase analytical column C18 HPLC system was employed. In the mobile phase, which was carried out in the ratio of 65:35 to 35:65 solvent-1, acetonitrile was employed as solvent number one and distilled water as solvent number two. The flow rate was 1.2 mL/min. Mometasone and itraconazole concentrations in the sample were estimated to be 250 nm.(33)(34)

In vitro drug release: Franz diffusion cells with porous membranes were used to investigate the drug's release pattern from the developed nano-gel for in vitro drug release research. All seven nano-gel formulations—F1 to F7—were sprayed onto the membrane's surface. A 1% weight-to-volume phosphate buffer solution of saline had already been added to the receiver compartment of the Franz diffusion cell.(35) The Franz diffusion cell's receiver compartment, it was swirled at 350 RPM and pre-filled with 1% w/v phosphate buffer saline with a pH of 7.4. The temperature in the Franz diffusion cell was maintained at 37 °C. According to the schedule, samples were obtained at intervals of 0, 1, 2, 4, 6, and 8 hours. Each time, 0.5 ml of the sample was removed and precisely equal amounts of fresh buffer solution were added in its place.(36) The drug sample was examined using the HPLC technique. The Malvern Master sizer 2000 MS and the polydispersity index (PDI) were used to determine the size distribution and mean particle size of

the (Itraconazole and Mometasone) nanogel. The mean particle size and size distribution of the produced samples were assessed in triplicate.(37)

Diffraction of X-rays (XRD): The structural characteristics of gelatin, untreated (Itraconazole and Mometasone), and nanogel were all examined using an X-ray diffractometer. 40 kV of voltage and 35 mA of current were used. Spanned a range of angles within the range of 5° and 60°. A number of typical peak heights in the diffraction patterns of binary or dualistic systems were compared with a reference peak height to determine the relative degree of crystallinity.(38)(39)

Differential Scanning Calorimetry (DSC) and Thermo Gravimetric Analysis (TGA) Gelatin, Itraconazole & Mometasone, and Nano gel’s heat stability were examined using thermo-gravimetric analysis. The material was tested in a nitrogen-filled chamber. The scan's flow rate was 20 ml/min, and the temperature was raised from ambient to 800 °C at a rate of 90 c/min. With heating rates of 10 °C/min and scanning temperatures of 400 °C, differential scanning calorimetry was used.(40)(18)

Studies on stability: The stability study adhered to ICH recommendations. The seven nanogel samples were stored for three months at ambient (30°C and 65% RH) and accelerated (40°C and 75% RH). After that, the vials were visualized to evaluate the clarity and look of the nanogel.

Antifungal activity in vitro: To test the Itraconazole & Mometasone -loaded Nano gel’s antifungal activity against Candidiasis albicans, the previously disclosed method was slightly changed. It was determined what the mean inhibition zone (ITZ) is. To calculate the antifungal activity, the value of ITZ was employed as an indication.(41)

Fungal inoculum: The following day, a culture of Candidiasis albicans was collected and stored in lab. After 12 hours, sterile 0.9% saline solution was used to dilute it, resulting in cultures containing 106 colony-forming units/mL of the bacteria.

Plating diffusion technique: We contrasted a control sample with nanogel that had Itraconazole & Mometasone added to it. The 1% w/w candidiasis inoculum was created in the petri plates

with 20 mL of dextrose agar. The candidiasis inoculum was injected into the petri plates in a 200 L volume. After the plates had been inoculated, they were allowed to dry for 30 minutes at room temperature. Each well was sliced and injected with 75 mg of Itraconazole & Mometasone nanogel. Well-equipped plates containing Itraconazole & Mometasone nanogel were stored at 36°C/2°C for one day. The microorganisms' inhibitory zone measurements around the wells were taken, and the outcomes were estimated. For each one, three measurements were taken.

Infrared spectroscopy using Fourier transforms (FT-IR): FT-IR spectrometer was used to record the FT-IR spectra of Itraconazole and Mometasone in raw, gelatin, and loaded nanogel forms. With 32 scans per sample, drugs, polymers, and nanogel were all s SEM, or scanning electron microscopy

SEM, or scanning electron microscopy: Scanning electron microscopy was used to evaluate the Itraconazole and Mometasone Nano gel’s surface structure and form. The nanogel was ground into a powder, and the dried powder was sonicated in water (1 mg/ml) for 10 minutes before being cast onto a glass slide and dried. By using a 10 kV acceleration voltage, a scanning electron microscope was able to anticipate its shape and surface morphology canned between 4000 cm1 and 400 cm 1.

Average particle size, polydispersity index (PDI): The size distribution and mean particle size of the Itraconazole and Mometasone nanogel were assessed using the Malvern Master sizer 2000 MS and the polydispersity index (PDI). The prepared samples' mean particle size and size distribution were measured in triplicate.

Diffraction of X-rays (XRD): Using an X-ray diffractometer, Gelatin, Itraconazole & Mometasone raw, and nanogel's structural analysis was completed. 35 mA of current and 40 kV of voltage were employed covered a spectrum of angles from 5° to 60°. By comparing a small sample of typical peak heights in the diffraction patterns of the binary or dualistic systems with a reference, the relative degree of crystallinity (RDC) was determined.

Thermo Gravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) Thermogravimetric analysis was used to assess the heat stability of gelatin, itraconazole &

mometasone, and nanogel. In a chamber filled with nitrogen, the substance was examined. The scan was conducted with a flow rate of 20 ml/min at a rate of 9 °C min-1 from the ambient temperature and escalated to 800°C. Differential scanning calorimetry was used, with heating rates of 10 °C/min and scanning temperatures of 400 °C.

Studies on Stability: All seven prepared formulations of Itraconazole &Mometasone Nano gel had their average particle sizes evaluated during stability testing in accordance with ICH guidelines. Nothing was altered in terms of clarity or look almost everything was the same as it had been at zero time. The Nano gel's particle size did not change over the course of ambient storage. The Nano gel's particle size rose under the accelerated storage circumstances, nevertheless, from 210 nm to 305, 380, and 520 nm at the end of the first, second, and third months, respectively. This demonstrated that as storage temperature was raised, particle size increased.

Antifungal activity in vitro: Numerous skin conditions have been linked to Candidiasis albicans. In order to evaluate the in vitro antifungal activity of itraconazole loaded Nano gel, Candidiasis albicans was utilized as the reference standard during the research. After applying Itraconazole & Mometasone Nano gel (2% w/w) to the wells, the mean diameter of the mean inhibition zone of the plates was measured. Compared to a placebo that didn't contain mometasone or itraconazole (0.410.04), Nano gel (2% w/w) demonstrated considerable antifungal activity (34.330.79). Increased physicochemical properties of miconazole following its inclusion in Nano gel system were substantiated by Itraconazole and Mometasone-loaded Nano gel has greater in vitro antifungal activity as compared to blank, or having no antifungal drug.

Average particle size, PDI: The produced PDI Nano gel has average particle sizes in the nm ranges. Figure 5 depicts the poly dispersibility index. It had a value of 0.337 and was visible in the outcome, demonstrating that the formulas' particle size distributions were diverse. The size ranges of the manufactured Nano gel as observed were between 207 nm and 2601 nm.

If the Nano gel loaded with Itraconazole & Mometasone formed, the X-Ray Diffraction (XRD): Itraconazole & Mometasone's nano gel diffraction pattern could be distinguished from the superimposition of each component. Investigation of variations between the solid state and gel produced can be aided by X-ray diffractometer.

By contrasting the various peak heights in the binary system's diffraction pattern with the reference, crystallinity has been deduced. The prepared Itraconazole & Mometasone, gelatin, and Nano gel X-ray diffraction patterns are depicted in figures 6a, 6b, and 6c, respectively. The presence of multiple prominent peaks at the following diffraction angles (2) of 13.0°, 14.8°, 22.4°, 25.4°, 28.5°, 30.5°, 31.5°, and 32.6° in the Itraconazole & mometasone X-ray diffractogram indicates that crystalline form of the drug is present.

Discussion: In this article, we offer a modified emulsification-diffusion method for creating biodegradable nanogel that are loaded with Mometasone and Itraconazole. Gelatin was added in increasing volumes in addition to chitosan, which had previously been used in smaller amounts. A high-speed homogenizer was used to introduce Nanogel to the aqueous phase at an approximate 8000 RPM speed. The aqueous phase containing Nanogel was mixed with the organic solution. After being continuously stirred at 10,000 rpm for 15 minutes, the resulting dispersion was sonicated for 15-20 minutes. Lecithin, a gelling agent, was added as a result, creating Nano-dispersion that was later converted into Nano gel (Wu et al., 2010). The created formulations produced clear Nano gel with good transparency, spread ability, consistency, and flow properties. The ready formulations demonstrated clear Nano gel with good consistency, spread ability, transparency, and flow characteristics.

The rheological studies unmistakably shown that viscosity rose as gelatin concentration increased and vice versa. Accordingly, it was discovered that the viscosity of the Nano gel formulations was directly related to the amount of gelatin included in the formulas. By using the plate diffusion method, in vitro antifungal activity was examined. Fungal cultures were first cultivated before Nano gel was inserted onto the plate. Fungus growth is slowed down by Nano gel. It was calculated by measuring the average ITZ diameter and adding extra gelatin polymer.

Studies on the in vitro release of drugs have shown that formulations F1, which contained more chitosan and had a pH of 7.4, released drugs at a greater rate than formulations with less chitosan.

According to stability studies, the generated Nano gel was stable under normal storage circumstances, but they clustered when the temperature was raised. The deep valley in the region of the produced Nano gel’s FTIR spectrum between 3600 and Stretching vibrations of the free -OH and -NH amide groups in gelatin and the imidazole group in itraconazole may cause a frequency of 3000 cm-1. A large valley is formed when -NH stretching vibrations overlay -OH stretching vibrations. The characteristic Peaks of Itraconazole and mometasone gelatin were found at 2922 cm-1 and 2850 cm-1, respectively. (C-H stretching).

According to SEM results, some of the manufactured Nano gel was in the shape of clusters, while Itraconazole & Mometasone had been distributed primarily uniformly throughout the Nano gel. According to observations, the generated Nano gel’s average particle size ranges were 207 nm, and the resulting poly dispersibility index (PDI) value was 0.337.The medication was found to be present in a crystalline form, according to the XRD data. The peak intensity of Nano gel decreased, indicating that the Itraconazole & Mometasone crystallinity had been lost. Gelatin, which is amorphous in form, was likely present at the time. The creation of a novel co-graft polymer was confirmed by TGA and DSC analysis. High thermal stability was demonstrated in the cross-linked Nano gel. The DSC peaks showed that the Nano gel was losing water before decomposing at about 340°C. It is evident that our process for making Nano gels produces cross-linked Nano gel that is thermally stable.

CONCLUSION:

A modified emulsification-diffusion process was used to successfully create a topical Nano gel that was loaded with Itaconazole & Mometasone. The generated Nano gel particles were found to be spherical through scanning electron microscopy research, however no crystalline drug structure was found in the finished Nano gel formulation, according to DSC research. Both the medication and the polymer had been integrated, according to FTIR tests, into the created

nanogel. The physicochemical characteristics of Nano gel demonstrated its suitability for topical application. The produced Nano gel’s antifungal efficacy was demonstrated in vitro, slowing the growth of Candida *albicans*.

List of Abbreviations:

SEM	Scanning Electron Microscopy
P-XRD	X-Ray Powder Diffraction
DSC	Differential Scanning Calorimetry
FT-IR	Fourier Transform Infrared Spectroscopy
UV	Ultra-Violet
TGA	Thermo Gravimetric Analysis
PDI	Poly Dispersibility Index
ITZ	Itraconazole
RPM	Revolution Per Minute
ANOVA	Analysis of variance

REFERENCES:

1. Raugi G, Nguyen TU. Superficial Dermatophyte Infections of the Skin [Internet]. Netter’s Infectious Disease. Elsevier Inc.; 2012. 102–109 p. Available from: http://dx.doi.org/10.1016/B978-1-4377-0126-5.00022-7

2. Hassan SE, Fouda A, Saied E, Farag MMS, Eid AM, Barghoth MG, et al. Rhizopus oryzae-Mediated Green Synthesis of Magnesium Oxide Nanoparticles (MgO-NPs): A Promising Tool for Effluent Treatment. J Fungi. 2021;8(5):1–25.

3. El-Yazbi AF, Aboukhalil FM, Khamis EF, Youssef RM, El-Sayed MA. Simultaneous determination of Mometasone Furoate and salicylic acid in complex matrix using green analytical method. Microchem J. 2021;163:105900.

4. Srivastava S, Mishra MK, Dubey NK. Nano formulation of Itraconazole And Mometasone For The Treatment Of Research Article Nano formulation of Itraconazole And Mometasone For The Treatment Of Topical Fungal Infection. 2020;(September).

5. Sindhu RK, Gupta R, Wadhera G, Kumar P. Modern Herbal Nanogels: Formulation,

Delivery Methods, and Applications. Gels (Basel, Switzerland). 2022 Feb;8(2).

6. Idumah CI, Nwuzor IC, Odera RS. Recent advances in polymer hydrogel nanoarchitectures and applications. Curr Res Green Sustain Chem [Internet]. 2021;4(March):100143. Available from: https://doi.org/10.1016/j.crgsc.2021.100143

7. Sousa F, Ferreira D, Reis S, Costa P. Current Insights on Antifungal Therapy: Novel Nanotechnology Approaches for Drug Delivery Systems and New Drugs from Natural Sources. Pharmaceuticals (Basel). 2020 Sep;13(9).

8. Li C, Obireddy SR, Lai W-F. Preparation and use of nanogels as carriers of drugs. Drug Deliv [Internet]. 2021 Jan 1;28(1):1594–602. Available from: https://doi.org/10.1080/10717544.2021.1955042

9. Talele S, Nikam P, Ghosh B, Deore C, Jaybhave A, Jadhav A. A research article on nanogel as topical promising drug delivery for diclofenac sodium. Indian J Pharm Educ Res. 2017;51(4):S580–7.

10. KA W, PP I, RO S. Preparation of itraconazole nanoparticles and its topical nanogel: Physicochemical properties and stability studies. Int J Pharm Sci Dev Res. 2019;(January):001–8.

11. Nami S, Aghebati-Maleki A, Aghebati-Maleki L. Current applications and prospects of nanoparticles for antifungal drug delivery. EXCLI J. 2021;20:562–84.

12. Madan JR, Khude PA, Dua K. Development and evaluation of solid lipid nanoparticles of mometasone furoate for topical delivery. Int J Pharm Investig. 2014 Apr;4(2):60–4.

13. Far J, Abdel-Haq M, Gruber M, Abu Ammar A. Developing Biodegradable Nanoparticles Loaded with Mometasone Furoate for Potential Nasal Drug Delivery. ACS omega. 2020 Apr;5(13):7432–9.

14. Muniraj S, S NT, R BD. Preparation and Characterization of Nanogel Drug Delivery System Containing Clotrimazole an Anti-Fungal Drug". Indo Am J Pharm Res [Internet]. 2020;10(07):2020. Available from: www.iajpr.com

15. Barreiro-Iglesias R, Alvarez-Lorenzo C, Concheiro A. Incorporation of small quantities of surfactants as a way to improve the rheological and diffusional behavior of carbopol gels. J Control Release [Internet]. 2001;77(1):59–75. Available from: https://www.sciencedirect.com/science/article/pii/S0168365901004588

16. Safitri FI, Nawangsari D, Febrina D. Overview: Application of Carbopol 940 in Gel.

2021;34(Ahms 2020):80–4.

17. Nesseem D. Formulation and evaluation of itraconazole via liquid crystal for topical delivery system. J Pharm Biomed Anal. 2001 Nov 1;26:387–99.

18. Akdag Y, Gulsun T, Izat N, Oner L, Sahin S. Formulation and characterization of mometasone furoate and formoterol fumarate containing dry powder inhaler by spray drying and homogenization methods. J Res Pharm. 2022;26(2):383–96.

19. Kasar PM, Kale KS, Phadtare DG. FORMULATION AND EVALUATION OF TOPICAL ANTIFUNGAL GEL CONTAINING ITRACONAZOLE. Int J Curr Pharm Res. 2018;

20. Kumar I, Thakur B, Sharma A, Thakur R. FORMULATION AND EVALUATION OF HERBAL OIL-BASED ITRACONAZOLE CREAM FOR FUNGAL INFECTION. Asian J Pharm Clin Res. 2020;

21. Dwivedi K, Mishra MK, Dubey NK, Pandey R. Nano Formulation Of Itraconazole And Its Synergism Against Candida Albicans When Combined With Silver Nanoparticle. In 2021.

22. Verma G, Mishra MK. Pharmaceutical Preformulation Studies in Formulation and Development of New Dosage Form: A Review. Int J Pharma Res Rev. 2016;5(10):12–20.

23. Qi H, Chen W, Huang C, Li L, Chen C, Li W, et al. Development of a poloxamer analogs/carbopol-based in situ gelling and mucoadhesive ophthalmic delivery system for puerarin. Int J Pharm [Internet]. 2007;337(1):178–87. Available from: https://www.sciencedirect.com/science/article/pii/S0378517307000063

24. Kaur D, Raina A, Singh N. Innovare Academic Sciences FORMULATION AND EVALUATION OF CARBOPOL 940 BASED GLIBENCLAMIDE TRANSDERMAL GEL. 2014;6(8).

25. Gummadi S, Varanasi S. UV spectrophotometric method development and validation for determination of an antifungal agent in bulk and capsules. Samson Isr /J Glob Trends Pharm Sci [Internet]. 2019;1(1):11–7. Available from: https://www.jgtps.com/admin/uploads/Mc49a0.pdf

26. Nurman S, Yulia R, Irmayanti, Noor E, Candra Sunarti T. The Optimization of Gel Preparations Using the Active Compounds of Arabica Coffee Ground Nanoparticles. Sci Pharm [Internet]. 2019;87(4). Available from: https://www.mdpi.com/2218-0532/87/4/32

27. Lefrançois P, Ibarboure E, Bruno P, Gontier E, Le Meins J-F, Schatz C. Insights into Carbopol gel formulations: Microscopy analysis of the microstructure and the influence of polyol additives. J Appl Polym Sci. 2015 Aug 1;132.

28. Setia A, Ahuja P. Chapter 8 - Nanohydrogels: Emerging trend for drug delivery. In: Grumezescu AM, editor. Organic Materials as Smart Nanocarriers for Drug Delivery [Internet]. William Andrew Publishing; 2018. p. 293–368. Available from: https://www.sciencedirect.com/science/article/pii/B9780128136638000087

29. Mahant S, Kumar S, Nanda S, Rao R. Microsponges for dermatological applications: Perspectives and challenges. Asian J Pharm Sci. 2020 May;15(3):273–91.

30. Kolimi P, Youssef A, Narala S, Nyavanandi D, Dudhipala N, Bandari S, et al. Development and characterization of itraconazole non-aqueous creams for the treatment of topical fungal infections. J Drug Deliv Sci Technol. 2022 Sep 1;76:103818.

31. Solanki N, Gupta SS, Serajuddin ATM. Rheological analysis of itraconazole-polymer mixtures to determine optimal melt extrusion temperature for development of amorphous solid dispersion. Eur J Pharm Sci [Internet]. 2018;111:482–91. Available from: https://www.sciencedirect.com/science/article/pii/S0928098717305900

32. Paul SD, Sharma H, Jeswani G, Jha AK. Chapter 12 - Novel gels: implications for drug delivery. In: Andronescu E, Grumezescu AM, editors. Nanostructures for Drug Delivery [Internet]. Elsevier; 2017. p. 379–412. (Micro and Nano Technologies). Available from: https://www.sciencedirect.com/science/article/pii/B9780323461436000129

33. Kumar A, Dua JS. FORMULATION AND EVALUATION OF ITRACONAZOLE NIOSOMAL GEL. Asian J Pharm Res Dev. 2018 Oct 31;6:76–80.

34. Lamie C, Elmowafy E, Ragaie MH, Attia DA, Mortada ND. Assessment of antifungal efficacy of itraconazole loaded aspasomal cream: comparative clinical study. Drug Deliv. 2022 Dec;29(1):1345–57.

35. KA W, PP I, RO S. Preparation of itraconazole nanoparticles and its topical nanogel: Physicochemical properties and stability studies. Int J Pharm Sci Dev Res. 2019;5:001–8.

36. Sadozai SK, Khan SA, Baseer A, Ullah R, Zeb A, Schneider M. In Vitro, Ex Vivo, and In Vivo Evaluation of Nanoparticle-Based Topical Formulation Against Candida albicans Infection. Front Pharmacol. 2022;13:909851.

37. Ahmed MM, Fatima F, Anwer MK, Ibnouf EO, Kalam MA, Alshamsan A, et al. Formulation and in vitro evaluation of topical nanosponge-based gel containing

butenafine for the treatment of fungal skin infection. Saudi Pharm J SPJ Off Publ Saudi Pharm Soc. 2021 May;29(5):467–77.

38. Gajra B, Dalwadi C, Patel R. Formulation and optimization of itraconazole polymeric lipid hybrid nanoparticles (Lipomer) using Box Behnken design. Daru. 2015 Jan;23(1):3.

39. Nakarani M, Misra AK, Patel JK, Vaghani SS. Itraconazole nanosuspension for oral delivery: Formulation, characterization and in vitro comparison with marketed formulation. Daru. 2010;18(2):84–90.

40. Badawi AA, El-Nabarawi MA, El-Setouhy DA, Alsammit SA. Formulation and stability testing of itraconazole crystalline nanoparticles. AAPS PharmSciTech. 2011 Sep;12(3):811–20.

41. Ho HN, Le TG, Dao TTT, Le TH, Dinh TTH, Nguyen DH, et al. Development of Itraconazole-Loaded Polymeric Nanoparticle Dermal Gel for Enhanced Antifungal Efficacy. J Nanomater. 2020;2020.

Figure Legend:

Figure:1- Mometasone Chemical Structure

Figure:2- Itraconazole Chemical Structure

Figure:3- X-Ray Diffraction of Itraconazole

Figure:4- X-Ray Diffraction of Mometasone

Figure:5- SEM Report of Itraconazole

Figure:6- SEM- Report of Mometasone

Figure: 7- Itraconazole Calibration Curve using a basic UV Spectroscope

Figure: 8- Mometasone Calibration Curve using a basic UV Spectroscope

Table Legend:

Table 1 - Amount of Ingredients taken for formulation development

Table 2 - Preformulation parameters for Itraconazole

Table 3 - Preformulation parameters for Mometasone

Table 4- Solubility of drug in different medium

Table 5- pH of formulations

Table 6- Viscosity of formulations

Table 7- Formulations Spreadibility:

Table 8- Extrudability of formulations:

Table 9- Entrapment efficiency:

Table 10-Absorbance reading of Itraconazole in methanol at λ max 262 nm

Table 11-Absorbance reading of Mometasone Furoate in methanol at λ max 248 nm