International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

Design Development and Evaluation on Microemulsion Gel of Itraconazole

*Rahul Tomar(Review Scholar), Mr. Vivek Verma(Assistant Professor),Mr. Maneesh Kumar Singh (Assistant Professor)
IIMT College of Medical Sciences,
IIMT University Meerut, U.P, India.

Submitted: 15-08-2022 Accepted: 24-08-2022

ABSTRACT
It was found that the drug showed good stability at the opted appropriate condition. For preparation of micro simulation for Itraconazole various oils, surfactants, and co-surfactants were screened via drug solubility study and a drug having maximum solubility selected for micro-emulsion preparation. By bearing the above result, we able to conclude that our drug Itraconazole was incorporated with success into the topical gel construction among all the built formulation the formulation F1 manifest better spread ability, drug content, viscosity, and drug liberation studies. Therefore, this was ceased that our formulation would be very assuring topical alternative for the treatment of skin fungal infections. Micro-emulsion successfully increased the permeation of the Itraconazole. Batch F4 was selected as optimized micro-emulsion loaded with Itraconazole.

Keywords: Topical Gel Itraconazole, Fungal Infections, Microemulsion

I. INTRODUCTION:

Itraconazole (ITZ), an azole antifungal agent, is widely used clinically for a variety of serious fungal infections in normal and immunocompromised hosts, including Aspergillosis, Cryptococcus, Candida, Blastomyces, disseminated Penicillium mameffei infections and Histoplasma capsulatum var. capsulatum. ITZ acts by impairing the synthesis of ergosterol, the essential component of the fungal cell membrane. The log partition coefficient of ITZ is 5.66 in a system of n-octanol and an aqueous buffer solution at pH 8.1, which indicates the hydrophobicity of the drug. ITZ is a weak base with a pKa of 3.7, and relatively insoluble in water [1, 2, 3, 4].

It has been used successfully in the treatment and prevention of Aspergillus infections with a lower toxicity than amphotericin B, indicating a better therapeutic index. However, the bioavailability of ITZ from the existing market formulation like the pellet capsule form is very low in neutropenic patients and inadequate plasma concentrations are found in patients receiving antineoplastic therapy. Topical drug delivery opens up a number of opportunities with regard to efficient drug therapy for fungal infection and would be more effective in these individuals. A topical application may be helpful for many neutropenic and other immunocompromised patients who have difficulty swallowing the oral capsule formulation. On the other hand, Oral Solution (Sporanox) is forbidden to be used in patients with impaired renal function, not because of the toxicity of the drug itself, but the adjuvant hydroxypropyl β-cyclodextrin (HP-β-CD). Each mm of Oral Solution (Sporanox) contains 10mg of ITZ solubilised by 400 mg of HP-β-CD as an inclusion complex. Following a single dose of 200 mg Oral Solution (Sporanox) to the subjects with severe renal impairment, clearance of HP-β-CD was six-fold reduced compared with subjects with normal renal function. Although its clinical relevance is unknown, it has been reported that HP-β-CD produces pancreatic adenocarcinoma in a rat carcinogenicity study [5 - 9].

Potential advantages of topical administration route include site directed delivery, which can obviate the need for oral and other systemic treatments and can reduce the total drug dose, thereby reducing non target site toxicities. A useful case in point is the treatment of cutaneous fungal infections where many useful agents must be administered orally to achieve clinically relevant cure rates [10-15].

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

II. MATERIALS AND METHODS:

Table.1: List of Chemicals

S.No.	Chemicals	Brand
1	Drug (Itraconazole)	Jubilant Life Sciences Roorkee
2	Oleic Acid	Nova Polychem Karol Bagh, New Delhi
3	Tween-20	S.D Fine chemicals Ltd, Mumbai, India
4	Propylene Glycol	-
5	Methanol	-

Table.2: List of Equipments Used

S.No.	Equipments	Manufacturer	Use
1	UV-Visible double beam Spectrophotometer	Shimadzu UV 1700	To measure the absorbance of the sample
2	Electronic Balance	Sortorius Single Pan	For weighing purpose
3	Magnetic Stirrer	Remi equipment, Mumbai.	Microemulsions preparation
4	pH meter	Elico L 1120	To measure the pH of the solution
5	Brookfield Viscometer	LVII model	To measure the viscosity
6	FTIR	Perkin Elmer	Compatibility study
7	Optical microscope	Nikon U.S	To identify the formulations
8	AFM	Commercial Nanoscope III Digital Instruments, Veeco.	Surface morphology and the particle size
9	TEM	Topcon, Paramus, NJ	Morphology and shape
10	Cooling centrifuge	Remi	Phase separation study

Preformulation Studies:

Preformulation may be described as a stage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, pre-formulation studies are essential to characterize the drug for proper designing of the drug delivery system. The pre-formulation studies which were performing in this project include [16].

Description:

Organoleptic characters of drug was observed and recorded by using descriptive terminology.

Melting Point:

Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of the tube 2.5mm to 3.5mm, and packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until the temperature is about 30°C below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1°C to 2°C per minute until melting is completed.

Solubility Studies:

The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 10 mg of drug was a suspended separately in 10 ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table (17).

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

Table.3: Solubility Profile I.P. 1996

Descriptive term	Parts of solvent required for 1 part of solute.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10, 000
Practically insoluble of Insoluble	Greater than or equal to 10,000

Hygroscopic Nature:

Procedure:

2 gm of the test specimens were weighed accurately in Petri-dish and the weight were noted down. Then the test specimens were exposed to 75% RH at 40°C in environment stability testing camber and the other was kept at room temperature for 7 days period. The specimen was weighed after 7 days and the difference in weight was noted down (Table 22).

Identification of Drug Sample:

Finding the Absorption Maxima (λ max):

The absorption maxima were found for drug identification. Ultraviolet visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength on the type of electronic transition associated with the absorption [18].

Preparation of Phosphate Buffer Solution [pH 7.4] I.P 1996:

- 27.218 g of potassium dihydrogenortho phosphate was dissolved in 1000 ml of distilled water to give a 0.2N solution.
- 8 g of sodium hydroxide was dissolved in 1000ml of distilled water to give 0.2N solution.
- 1250ml of 0.2N potassium dihydrogenortho phosphate and 977.5ml of 0.2N sodium hydroxide were mixed together and made up to 5000ml with distilled water.
- The drug solution (10, 20, 30, 40, 50, 60µg/ml) in Phosphate buffer pH 7.4 was taken in standard cuvette, and scanned in the range of 200-300nm in a UV spectrophotometer.
- It exhibits maxima at 266nm. UV spectrum of drug taken in phosphate buffer pH 7.4 also exhibits maxima at 266nm. Therefore, further all measurements were taken at 266nm. The results are shown in fig 18.

Standard Curve:

Preparation of Standard plot for Itraconazole in Phosphate Buffer pH 7.4:

Accurately weighed amount of Itraconazole (5mg) was dissolved in small quantity of 0.1N NaOH & then diluted to 100ml with phosphate buffer pH 7.4. Each ml of the stock solution contains 100µg of Itraconazole. From this stock solution different standard of working standard solutions i.e., 10, 20, 30, 40, 50, 60µg/ml were made up with phosphate buffer pH 7.4 and the absorbance was measured at 266nm using phosphate buffer pH 7.4 as blank by UV spectrophotometric method. A graph is plotted by using concentration at X-axis and absorbance at Y-axis [19].

Fourier Transforms Infrared (FTIR) Spectral Analysis:

FTIR was used to identify the functional groups in the molecule. The drug is mixed with KBr disk was scanned at 4mm/s at a resolution of 2cm over a wave number region of 400 to 4000cm-1. The characteristic peaks were recorded. Drug-Excipient Compatibility Studies by FT-IR Analysis Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in therange of 4000-400 cm-1 using KBr disc method (Schimadzu IR-

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

Prestige-21) and observed for characteristic peaks of drug.

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrums of pure drug, Itraconazole, Oleic acid, tween-20, propylene glycol were obtained. After that admixtures of drug with other excipients were prepared and IR Spectra was obtained. The obtained spectra of physical admixtures was observed for major peaks and recorded. The results of this observation were concluded that there is no interaction between the drug (Itraconazole) & other excipients (Oleic acid, tween-20, propylene glycol) [20].

Method of Preparation of Topical Gel Containing Itraconazole:

Itraconazole (5% w/w) was dissolved in oily phase (Oleic Acid) consisting of equal amount of menthol. The Itraconazole solution was then mixed with mixture of surfactant- Tween-20 and co-surfactant (Propylene Glycol). Finally, an appropriate amount of water was added to the Itraconazole solution mixture drop by drop to get micro-emulsion (Yang et al., 2004). The composition of the different formulated micro-emulsion.

Table.4: Preparation of Topical Gel

S. No.	Ingredients	F1	F2	F3	F4	F5
1	Itraconazole	5	5	5	5	5
2	Oleic Acid	1	1.5	2	3	3
3	Tween-20	3	3	3	4	3
4	Propylene Glycol	2	2	2	2	2
5	Methanol	2	4	6	8	10
6	Final Volume H2O	50	50	50	50	50

Evaluation of Physicochemical Parameters of Prepared Itraconazole Gel:

Zeta Potential

Zeta potential was the measurement of attraction or repulsion in between particles. Its measurement brings details about the dispersion mechanism which is used to measure electrostatic dispersion. The zeta potential calculation is important limitation across a various range of industries incorporates pharmaceuticals, brewing, medicine, ceramics, and water treatment. For colloidal stability, the repulsive forces between two particles should be ascendant. Zeta potential was a useful index of magnitude for interaction between colloidal particles. In general, the colloidal systems stability was determined using measurements based on zeta potential [21, 22, 23, 24].

Determination of pH:

The digital pH meter is used to find out the pH value of a formulated topical gel. The values of prepared formulations are between the ranges of 4–8 that ignores the chance of skin irritation [25].

Spread Ability:

The assessment of spread capacity, two glass slides were taken, and the prepared gel was compressed in between the two glass slides to steady stability by applying weight and leaves it for 6 min. The value of spreadability is gathered by determining the time taken for the two glass slides to get separated [26].

Percentage Yield:

The practical yield of each sample is determined by weighing the empty container and the container along with the gel formulation and subtraction of empty container with the container along with the gel [27].

The expression “uniformity of dosage unit” is explained as the substances degree of uniformity among dosage units. The content uniformity test depends on the assay of the active medicament. 100 mg of the formulated gel is taken and dissolved in 100 ml of phosphate buffer of pH 6.8. The above solution is allowed to stand for 30 min followed by gentle stirring to enhance the solubility of the drug. Then, it is treated, and the absorbance of the solution was identified spectrophotometrically at 266nm using phosphate buffer pH 6.8 as blank [27].

Viscosity Estimation:

Alteration in viscosity of the product displays adjustment instability and efficacy of the product. Uniformity of formulation lies on the ratio of the solid fraction to liquid fraction which constructs gel structure. The viscosity of topical gels was acquired using Brook-Field viscometer

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

DE-V model using spindle no 61 and spindle speed of 50 rpm at 37°C.

In Vitro Drug Release Study:

Franz-diffusion cells equipment is used to study the in vitro drug release using various formulations. The specific quantity of formulation was applied on the membrane positioned between donor and receptor chambers with an available diffusion area. Fill the receptor chamber with phosphate buffer pH 6.8 and is blended repeatedly with a tiny magnetic bead, the speed of 50rpm is continued at the temperature at 37°C±2°C. At different meantime, the samples were taken and then it is exchanged with the same volume of phosphate buffer pH 6.8 to maintain the volume of dissolution medium. In all cases, sink conditions are seen. The obtained samples were analyzed spectrophotometrically at 266nm [26].

Stability Study:

The concentration of an active ingredient of all formulation may fall with upraise in the temperature and time. This assists in drop in the potency of the product. Stability study in various temperatures ought to be dispensed to anticipate the formulation stability. Stability studies are strenuous at regulating the outcome of aging and storage under divers circumstance on the formulated gel. Stability studies take place to detect whether any chemical breakdown of itraconazole formulations take place or not. The chief formulation was kept at 30±2°C and 40±2°C at RH 65±5 and 75±5 RH for 2 months in a glass vial. After 1 or 2 months, the samples were repeatedly tested for the drug content and in vitro release studies [24].

III. RESULTS AND DISCUSSION

Preformulation Studies:

Description:

Nature: White to off-white colour powder

Taste: Bitter

Melting point:

Table.5: Melting Point Determination

Drug	Melting Point	Normal Range
Itraconazole	170 ± 0.145	150-172

Solubility:

Table.6: Solubility Profile of Itraconazole

S. No	Solvents	Solubility
1	Distilled H2O	Slightly Soluble
2	Phosphate Buff. (Ph-&.4)	Very Soluble
3	CH3OH	-
4	C2H5OH	-
5	CCL4	Slightly Soluble
6	0.1N NaOH	-

Hygroscopic Nature:

Table.7: Hygroscopic Nature of ITZ

At Room Temp.	75%RH at40°C
Sample No-1	-
Wt. gain observed nil	Wt. gain observed nil

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

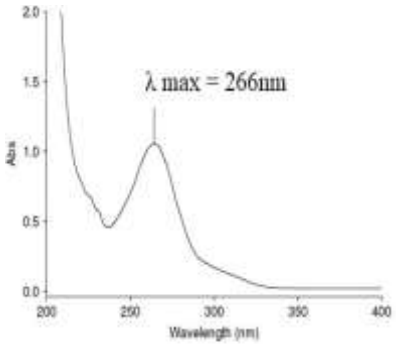

Fig.1UV spectrum of Lornoxicam in phosphate buffer pH 7.4

Table.8: Absorption maxima of ITZ in phosphate buffer pH 7.4

Solvent	**Conc.(µg)/ml**	**λ max (nm)**	**Abs.**
Phosphate buffer Ph7.4	50	266	0.6503

Standard Plot of ITZ in Phosphate Buffer pH 7.4:

Table.9: UV Absorbance of Phosphate Buffer pH 7.4

S.No.	**Conc.(µg)/ml**	**Abs. at 266nm**
1	10	0.1324
2	20	0.2243
3	30	0.3624
4	40	0.4776
5	50	0.5620
6	60	0.6503

1.3.8 Standard Plot of ITZ in Phosphate Buffer pH 7.4:

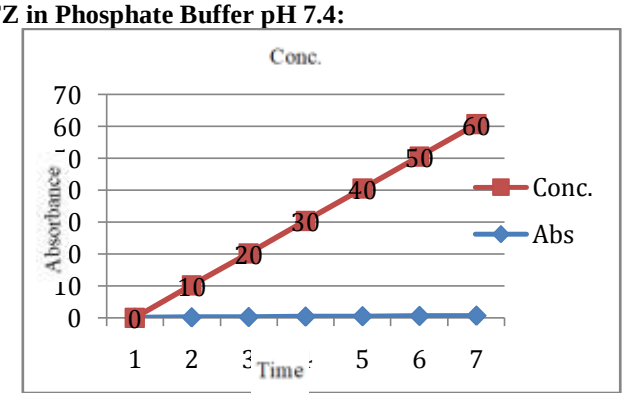

Fig.2 Standard Plot of ITZ in Phosphate Buffer pH 7.4

FTIR Study:

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

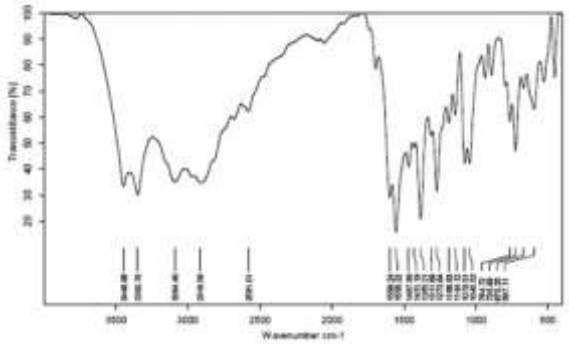

Fig.3: Fourier-Transform Infrared Spectrum of ITZ

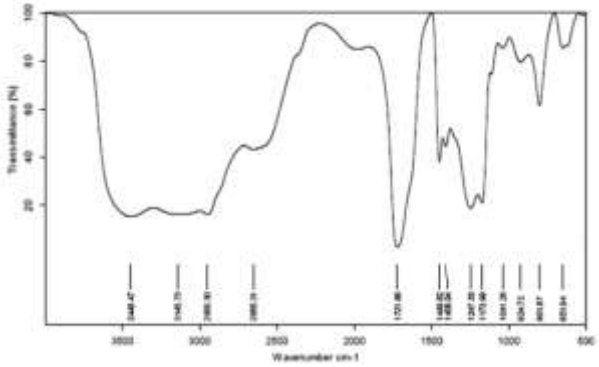

Fig.4: FTIR of Oleic Acid

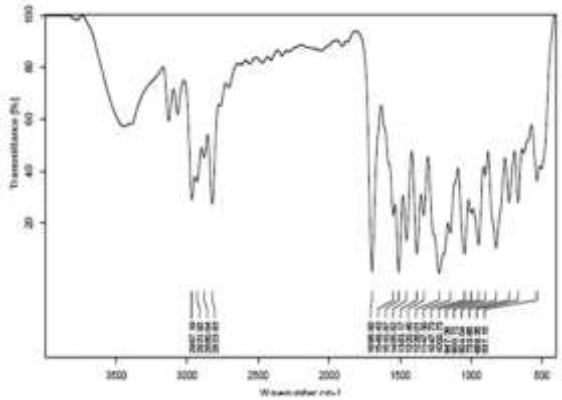

Fig.5: FTIR of Tween-20

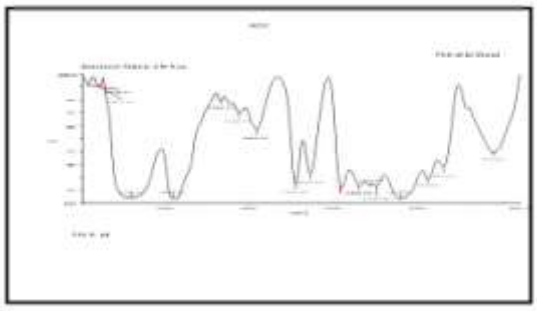

Fig.6: FTIR of Propylene Glycol

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

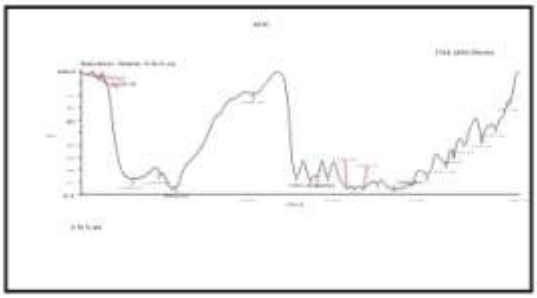

Fig.7: FT-IR of Physical Admixture 1. (ITZ + Oleic acid + Tween-20 + Propylene glycol)

Table.10: FT-IR Spectral Assignment of ITZ

Wavenumber in (cm-1)	Functional groups
3400.78	O-H stretching
3060.12	N-H stretching
2870.86	C-H(Aromatic) stretching
1596.16	Carbonyl –C=O stretching
1538.68	NH(Amide) stretching
1420.63	S=O stretching
1379.47	C-S Stretching
1238.55	C-O Stretching
2924.94	C-H Stretching
1715.82	C-O Stretching
1277.61	C-O Stretching
721.75	C-H Out of plane bending
3389.55	N-H Stretching in Primary amine
2932.48	C-H Stretching
837.76	C-O Stretching
664.32	C-H Out of plane bending
3409.62	O-H Stretching
2917.08	C-H Stretching
1251.70	C-O Stretching
3388.82	O-H Stretching
1722.10	C=O Stretching
1598.92	C-N Stretching

There are no extra peaks seen other than the normal peak in the spectra of the mixture of the drug & excipients & so there is no interaction with the drug & Excipients and they are compatible with each other. The IR spectra of the drug & polymer combination were compared with the spectra of the pure drug & individual Excipients in which no shifting of peaks was significantly found, indicating the stability of the drug during micro emulsion formulation development.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

Evaluation Parameter of ITZ Gel:

Table.11: Evaluation Parameter of ITZ Gel:

Formulation	PH	Zeta Potential	Spread ability	% Yield	Drug Content Uniformity	Viscosity Estimation
F1	7.2	13.4mV	10.67	96.43	97.56	2342
F2	6.9	11.3mV	11.09	96.98	98.45	3861
F3	7.0	13.5mV	11.96	98.76	96.86	4289
F4	6.7	14.3mV	11.76	99.10	98.96	4567
F5	6.8	12.2mV	10.26	97.42	98.32	5096

In-Vitro Skin Permeation Study:

Table.12: In-Vitro Skin Permeation Study

S. No	Time (min)	% Drug release				
		F1	F2	F3	F4	F5
1	30	12.32	15.41	16.65	18.54	18.23
2	60	23.56	25.43	24.65	30.24	29.87
3	90	35.76	36.78	35.65	42.45	38.76
4	120	50.87	49.87	46.87	56.76	47.35
5	150	62.87	59.90	60.10	68.98	56.26
6	180	73.65	71.54	71.34	79.41	70.92
7	210	82.67	85.65	85.61	87.43	81.36
8	240	92.45	95.85	96.87	98.96	92.90

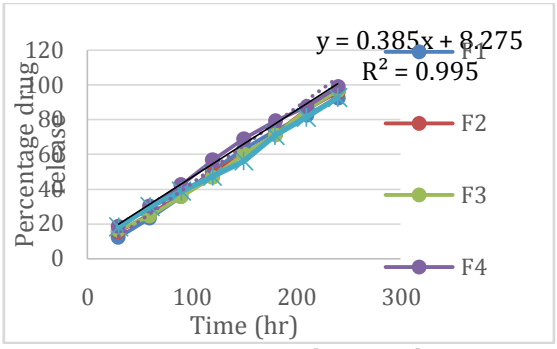

Fig.8: % Drug Release Study

The drug release profile of ITZ topical gel formulations was accomplished by diffusion cell. As an outcome of the in vitro release studies of all formulations are given in Table.12, and the statistically represented is shown in Fig.8.

The percentage drug release of all formulations after 4h using Oleic Acid and Tween-20 was identified to be 92.45% (F1), 95.85% (F2), 96.87% (F3), 98.96% (F4) and 92.90% (F5) respectively. The most essential factors in the drug release are the type of polymer by the concentration of polymer.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

Stability Study of F4 Optimized Formulation:

Table.13 Stability Study of Formulation 4

S. No.	Time (min)	0 Days	Percentage % drug release			
			30 days		60 days	
			30±2°C	40±2°C	30±2°C	40±2°C
1	30	18.54	18.95±0.13	18.95±0.03	18.94±0.05	18.94±0.15
	60	30.24	30.22±0.14	30.20±0.35	30.09±0.16	29.85±0.19
2	90	42.45	42.43±0.18	4 2.40±0.44	41.56±0.10	41.34±0.12
3	120	56.76	56.75±1.13	56.70±1.09	56.66±0.89	55.44±0.45
4	150	68.98	68.96±1.16	68.80±1.10	68.50±1.09	67.90±1.06
5	180	79.41	79.42±1.42	78.40±1.21	78.32±1.12	78.42±0.65
6	210	87.43	87.20±0.13	87.10±0.10	87.00±0.05	86.90±0.18
7	240	98.96	98.96±0.10	98.90±0.11	98.80±0.132	98.65±0.100

Table.14: Drug Content Estimation After Storing at Different Temperatures (F4)

S. No.	Formulation	Drug Content			
		30±2C		40±2C	
		30 days	60 days	30 days	60 days
1	F4	98.74±0.06	97.38±0.10	98.16±0.12	97.42±0.06

There was no noticeable difference in the in vitro drug release study F4 (from 98.96% to 96.80%) at 30±2°C at 65±5 RH. After storing at 40±2°C at 75±5 RH the in vitro drug release study of F4 formulation is decreased. The statistics are stated in Table 7. This was discovered that the developed itraconazole gel formulae and its storage were identified to be firm for 2 months at room temperature; there were no changes in the specification that is inflated such as physical aspect as color, drug content, and drug release during the inspection. Stability studies were carried for the most effective formulation-F4, at 30±2°C and 40±2°C at 65±5 and 75±5 RH for 2 months. At the end of 2 months, samples were evaluated. Drug content study showed that there was no major change in the content drug of F4 (from 98.74% to 98.39%) at 30±2°C at 65±5 RH and decrease at 40±2°C at 75±5 RH (from 97.38% to 97.42%). The data are presented in Table 8.

IV. DISCUSSION:

The triazole derivative of Itraconazole was one of the best drugs suited for the treatment of fungal infections. In this study, the topical gel preparation of Itraconazole was formulated for efficientthat transports the drug across the skin. UV spectrophotometry surveys of prepared itraconazole gel manifest the absorption at the wavelength of 266nm. The obtained FTIR peaks showed the drug-excipients compatibility. Different ratio of the formulation (F1, F2, F3, F4 and F5) was advanced using suitable Surfectant and Co-surfectant (Oleic acid + Tween-20 + Propylene glycol) and infiltration enhancer. Advanced formulations of itraconazole were analyzed for physiochemical parameters such as viscosity, spreadability, drug content, and in-vitro drug release studies. From all the build out formulation, F4 manifest drug liberates for a phase of 4h. The most efficient formulation of F4 shows a significant change in drug contents. The formulated drug stability was monitored for 2 months at 30±2°C and 65± 5 RH. It was found that the drug showed good stability at the opted appropriate condition.

V. CONCLUSION

For preparation of micro simulation for Itraconazole various oils, surfactants, and co-surfactants were screened via drug solubility study and a drug having maximum solubility selected for micro-emulsion preparation. By bearing the above result, we able to conclude that our drug Itraconazole was incorporated with success into the topical gel construction among all the built formulation the formulation F1 manifest better spread ability, drug content, viscosity, and drug liberation studies. Therefore, this was ceased that our formulation would be very assuring topical alternative for the treatment of skin fungal infections. Micro-emulsion successfully increased

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp:1785-1796 www.ijprajournal.com ISSN: 2456-4494

the permeation of the Itraconazole. Batch F4 was selected as optimized micro-emulsion loaded with Itraconazole.

REFERENCES:

[1]. Grant SM, Clissold SP. Itraconazole: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses. Drugs 1989;37:310-44.
[2]. Lortholary O, Denning DW, Dupont B. Endemic mycoses: A treatment update. J AntimicrobChemother 1999;43:321-31.
[3]. Van Cauteren H, Heykants J, De Coster R, Cauwenbergh G. Itraconazole: Pharmacologic studies in animals and humans. Rev Infect Dis 1987;9:S43-6.
[4]. Heykants J, Van Peer A, Van de Velde V, Van Rooy P, Meuldermans W, Lavrijsen K, et al. The clinical pharmacokinetics of itraconazole: An overview. Mycoses 1989;32:67-87.
[5]. Tricot G, Joosten E, Boogaerts MA, Vande Pi e J, Cauwenbergh G. Ketoconazole vs. itraconazole for antifungal prophylaxis in patients with severe granulocytopenia: Preliminary results of two nonrandomized studies. Rev Infect Dis 1987;9:S94-99.
[6]. De Beule K, De Doncker P, Cauwenbergh G, Koster M, Legendre R, Blatchford N et al. The treatment of aspergillosis and aspergilloma with itraconazole, clinical results of an open international study (1982-1987). Mycoses 1988;31:476-85.
[7]. Dupont B. Itraconazole therapy in aspergillosis: Study in 49 patients. J Am Acad Dermatol 1990;23:607-14.
[8]. Como JA, Dismukes WE. Oral azole drugs as systemic antifungal therapy. N Engl J Med 1994;330:263-72.
[9]. Bradford CR, Prentice AG, Warnock DW, Copplestone JA. Comparison of the multiple dose pharmacokinetics of two formulations of itraconazole during remission induction for acute myeloblastic leukaemia. J AntimicrobChemother 1991;28:555-60.
[10]. Thomson PDR, Montvale NJ. 59th ed. Montavale, NJ. Physician' Desk Reference;2005. p. 1757-66.
[11]. Schaefer H, Redelmeier TE. Prediction and measurements of percutaneous absorption. In: Schaefer H, Redelmeier TE, editors. Skin Barrier: principles of percutaneous absorption. Basel, Karge, 1996. p. 118-52.
[12]. Ghosh TK, Pfister WR, Yum SI, editors. Transdermal and Topical Drug Delivery Systems, Interpharm Press, Buff alo Grove, IL. 1997. p. 33-112.
[13]. Odds FC, Van Custem J. Itraconazole: Preclinical data in vitro and in vivo in cutaneous and other superficial mycoses. Clin Dermatol 1993;7:251-61.
[14]. Gupta AK, Neil NH. A risk-benefi t assessment of the newer oral antifungal agents used to treat onchomycosis. Drug Saf 2000; 22:33-52.
[15]. Rubin AI, Bagheri B, Scher RK. Six novel antimycotics. Am J Clin Dermatol 2002;3:71- 81.
[16]. Chien YW. Transdermal Drug Delivery and Delivery Systems, in: Y.W.Chien, Novel Drug Delivery Systems, 2nd ed, Chapter 7, Marcel Dekker, New York, 1992: 301-380.
[17]. Vyas SP and Khar RK. Targetted and Controlled Drug Delivery Novel Carrier System 1st ed., CBS Publishers and Distributors, New Delhi, 2002:411-447.
[18]. Hadgraft J, Guy R. In; Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel,35,296.
[19]. Arunachalam A, Karthikeyan M, Kumar VD, Prathap M, Sethuraman S, Ashutoshkumar S, Manidipa S. Transdermal Drug Delivery System: A Review. Current Pharma Res. 2010; 1(1):70- 81.
[20]. Raj, G. and Raveendran, R. (2019). Introduction to Basics of Pharmacology and Toxicology Volume 1: General and Molecular Pharmacology: Principles of Drug Action. Springer Nature Singapore Pte Ltd.
[21]. Prausnitz MR, Mitragotri S, Langer R. Current Status and Futyre Potential of Transdermal Drug Delivery. Nature Reviews, Drug Discovery, 2004; (3):115-124.
[22]. Govil SK, In; Tyle, P., Eds., Drug Delivery: Fundamentals and Application, Marcel Dekker, Inc., New York, 1998: 385-406.
[23]. Jain NK. Contolled and Novel Drug Delivery, Cbs Publisher and Distributor, 1st ed,100.
[24]. Hoar TP, Schulman JH, Transparent Water-In-Oil Dispersions, The Oleopathic Hydro-Micelle, Nature, 1943: 152; 102-103.
[25]. Schulman, J.H, Stoeckenius, W Prince, L.M, Mechanism Of Formation and Structure of Microemulsions By Electron Microscopy, J. Phys. Chem, 1959: 63,1677-1680.

[26]. Vyas SP, Khar RK. Submicron Emulsions in Targeted and Controlled Drug Delivery, Novel Carrier System; Cbs Publishers and Distributors, New Delhi, 2002: (282-302).
[27]. Jadhav KR. et al., Applications of Microemulsion Based Drug Delivery System. Curr Drug Deliv, 2006; 3(3):267-73.