RESEARCH PAPER

Formulation and evaluation of a microemulsion-based delivery system containing itraconazole

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ABSTRACT

The skin is immediately treated using topical medicines. Topical drug delivery systems fall into the following classes: lotions, ointments, creams, gels and emulsions. When put to use, it might be quite beneficial. Their large drug loading capacity allows them to give a greater concentration gradient in topical drug administration, increasing the driving force across the skin. Because of its low interfacial tension, the microemulsion will make excellent contact with the skin's surface and fill up tiny gaps and wrinkles. This improves medication transmission through the vehicle's skin. They have been applied to increase the bioavailability of a number of poorly soluble medications, such as antifungal medications used to treat fungal infections.

Keywords: Topical drug delivery, Microemulsion, Itraconazole, Anti-fungal.

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Introduction

In the pharmaceutical industry, topical drug delivery methods have grown to represent a prominent class. For a number of reasons, topical drug administration may be superior to other approaches. These include the avoidance of hepatic first-pass metabolism, salivary and stomach drug degradation, and associated toxicity effects, as well as the ease of administration and controllable drug delivery rate [1]. Enhance the cutaneous absorption of both hydrophilic and lipophilic active medicinal substances in topical preparations. To improve penetration, other strategies have been used, such as altering the characteristics of the medication, the vehicle, or the skin [2]. The use of topical products in treatment is growing in popularity and represents a significant class of medication delivery mechanisms. The topic of drug penetration into the skin is the subject of several investigations nowadays. They may improve the penetration of both lipophilic and hydrophilic medications. The skin irritant factor must be taken into account primarily when the product is meant to be administered for a longer duration of time, since the creation of microemulsion necessitates a high concentration of surfactant [3]. Applying a medication or formulation containing a medication topically to treat joint, soft tissue, and skin problems is known as topical delivery. Because it has direct access to the target location, it decreases systemic toxicity, offers a simple method of administration, provides substantial surface area, and delivers the medication in a sustained and regulated manner. It has increased patient acceptability and is administered painlessly [4]. Medications should penetrate the skin's layers to provide sufficient drug concentrations after topical delivery. Topical medicine delivery agents fall into two main categories: external topicals and internal topicals. Internal topicals are applied topically to the rectal region, vaginal area, or other areas for local action, whereas external topicals are sprayed or otherwise applied to the affected area to cover it. Several major benefits of topical drug delivery systems include avoiding first-pass metabolism, gastrointestinal incompatibilities, site-specificity, improved patient compliance, the possibility and ease of self-medication, and the ability to stop using drugs with a short half-life and narrow therapeutic index when necessary [5].

Topical dose forms are designed to comfortably administer medications to a specific region of the skin. Topical drugs are given directly to the part of the body that hurts, penetrating the skin. The peripheral tissues, such as soft tissue and peripheral nerves, immediately underneath the application site are where a topical drug acts. No clinically meaningful systemic drug concentration should be produced by topical medications that are prepared as gels, microemulsions, creams, liquids, or patches. traditional commercially available NSAID dose formulations for topical use [6]. The ability of microemulsions to solubilise poorly water-soluble drugs and to improve topical and systemic availability has led to their study as drug delivery systems. Microemulsions are stable, optically isotropic, single-phase systems of water, oil,

surfactant, and/or co-surfactant that have a low viscosity. It exhibits quick and effective skin penetration and aids in the solubilisation of the lipophilic drug moiety. Thus, topical medication administration benefits from it [7]. As a result, microemulsions with an average droplet diameter of 10–140 nm develop spontaneously. Compared to other traditional topical formulations including ointments, creams, gels, and lotions, the microemulsion's composition and structure allow it to integrate a larger quantity of medicine and can solubilise poorly water-soluble pharmaceuticals due to its tiny droplet size [8]. A triazole antifungal medication called itraconazole is used to treat a number of fungal diseases, including onychomycosis and blastomycosis. An antifungal drug called itraconazole stops fungal cell development and encourages fungal cell death [9]. Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, and Trichophyton species are among the organisms against which it has in vitro action.Inhibiting the fungal cytochrome P450 enzyme 14α-demethylase, which transforms lanosterol into ergosterol—a crucial component of fungal cell membranes—is how itraconazole exerts its antifungal action [10].

Materials and Methods

Preformulation investigations are conducted to ascertain the drug sample's purity while also identifying other characteristics that are crucial to the creation of the formulation. When developing a medication formulation, the physicochemical characteristics of the drug are crucial in determining how the drug interacts with the excipients and additives [10].

Determination of wavelength maxima (λ_{max})

The drug's structure was validated using the UV spectrophotometric technique. After precisely weighing and dissolving ITC (100 mg) and VRC (100 mg) in PBS (pH 7.4) in a 100 ml volumetric flask, the final volume was adjusted to 100 ml. To create a stock solution with a concentration of 100µg/ml, 10 ml of this solution was further diluted to 100 ml. A theoretical concentration of 10µg/ml was obtained by diluting a further 1 ml of stick solution with 10 ml of PBS (pH 7.4). To find the wavelength maxima, the solution (10µg/ml) was scanned in the 200–400 nm range using a UV-Visible spectrophotometer (Shimadzu 1601, Japan) [Figure 1].

Preparation of Calibration Curve

For the quantitative assessment of the medication, a calibration curve was created spectrophotometrically using the UV absorption of ITC at λmax 236 nm and VRC at λmax 256 nm in PBS (pH 7.4). To make a 1 mg/ml solution in PBS (pH 7.4), 100 mg of ITC and VRC were precisely weighed and added to a 100 ml volumetric flask. A theoretical concentration of 100µg/ml was obtained by mixing 10 ml of this solution (1 mg/ml) with 10 ml of PBS (pH 7.4). Using concentration vs. absorbance data, diluents of 2 to 20 µg/ml were produced and evaluated at λmax 236 nm for ITC (Figure 2).

Solubility

Itraconazole and voriconazole's solubility was assessed in water, methanol, and buffer by equilibrating the excess drug suspension in 5 ml of medium. The mixture was then gently shaken for 24 hours at 32ºC, centrifuged for 10 minutes at 3000 rpm, filtered, diluted, and examined using a UV spectrometer at λmax 236 nm for ITC.

Partition coefficients

The drug's polar and non-polar characteristics are shown by the partition coefficient. In a glass stoppered test tube, 100 mg of ITC and VRC were added to 10 ml of distilled water, followed by 10 ml of n-octanol, and shaken for 4 hours. A separating funnel and a UV spectrophotometer set to λmax 236 nm for ITC were then used to separate the aqueous phase.

$$Po/w = Co/Caq$$

where, Po/w = partition coefficient of drug, Co= concentration of drug in n-octanol,

Caq=concentration of drug in aqueous phase i.e. Distilled water.

Construction of pseudo-ternary phase diagrams

To find the microemulsion zone where microemulsion may be formed at any moment, a ternary phase diagram of the microemulsion was constructed using Sigma Plot version 11.0 software. To find out what the present microemulsion concentration range is, we used the water titration method at 25°C to make pseudo-ternary phase diagrams with different oil and surfactant:co-surfactant ratios. When the right microemulsion components were selected, a ternary pseudo phase diagram was drawn to define the microemulsion zones' dimensions and properties. A number of samples with different compositions need to be prepared for these kinds of designs. The microemulsion region is first defined by its low viscosity and isotropic composition. A ternary phase diagram in two dimensions was generated by maintaining a constant ratio of surfactant to co-surfactant. The oil phase that was examined had an HLB value of 1.0 and was oleic acid. The surfactant was Tween 80 with an HLB value of 15.0, and the co-surfactant was ethanol. Distilled water made up the liquid phase. A 1:1, 2:1, and 3:1 weight ratio of Tween 80 to ethanol were used to construct three phase diagrams, respectively. All of the phase diagrams were adjusted by changing the oil-to-surfactant/co-surfactant ratios to the following: 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 2:8, and 1:9. The oily mixtures were heated to 37°C and stirred continuously while water was added drop by drop

until the mixture became clear. Titration was considered complete when a turbidity or haziness of the solution was seen. It was noticed how much of the watery phase was needed to get the combination turbid. Next, the percentages of the various included pseudo phases were computed. Initial microemulsion testing batches were shown with oil phases ranging from 10 to 90% in each batch [11]. Phase diagrams are used to show the clear microemulsion area. The microemulsions with a Tween 80: Ethanol (1:1) concentrations in the A6 medication itraconazole was found to have the maximum microemulsion zone and were optimized for formulation and assessment. When examined for optical clarity against intense light, all of the microemulsions that produced were clear and looked like a homogeneous single-phase liquid.

Optimized final batch

For the ITC loaded microemulsion formulation, the ternary phase diagrams of oil (oleic acid) and surfactant (Tween 80)/co-surfactant (ethanol) in a 1:1 ratio were used at A6. In order to identify the microemulsion area and identify the potential for creating microemulsions with various possible compositions of water, surfactant/co-surfactant, and oil, microemulsion systems were generated using the titration technique. ITC was mixed with oil, followed by a drop-by-drop addition of the surfactant and co-surfactant combination (Smix 1:1), water, and a magnetic stirrer to create a homogenous dispersion or solution. The point at which the solution becomes hazy or turbid was the titration's finish. In order to create a microemulsion, the amount of the aqueous phase needed to make the combination turbid was recorded. Table 3 [12–13] displays the optimised composition of the ITC (A6) loaded microemulsion.

Table 1: Composition of ITC loaded microemulsion

S. No.	Materials	Quantity
1.	Drug Iraconazole	50 mg
2.	Oleic acid	6 ml
3.	Tween 80	2ml
4.	Ethanol	2ml
5.	Water	q. s.

Evaluation of microemulsion

Optical Transparency

The microemulsion is diluted fifty to one hundred times. By using a UV/Visible spectrophotometer to measure the proportion of light transmitted at a wavelength of 400–800 nm, optical clarity was evaluated both visually and spectrophotometrically. The formulation's percentage transmittance is noted.

pH

The microemulsion's appropriateness for topical application is indicated by its pH value. A digital pH meter (Equiptronics, 111E, India) was used to measure the microemulsion's pH in order to verify that the created microemulsion matches that of human skin, making it more palatable. The pH final preparation and administration route are determined by the excipients included in the formulation. The measured pH values of the microemulsion formulations ranged from 5.3 to 6.5 A6, which is the ideal pH for topical administration on skin.

Drug content

Ten millilitres of methanol were placed in a beaker with one millilitre of microemulsion formulations. After 30 minutes of stirring, the contents of the beaker were left for 24 hours. The contents of the beaker were moved into a centrifuge tube after 24 hours, and they were spun for 10 minutes at 3000 rpm. The supernatant was filtered and separated. The drug concentration was then determined spectrophotometrically after 0.1 ml of the supernatant had been suitably diluted with PBS pH 7.4 [14].

$$\text{Drug content (\%)} = \frac{\text{Actual amount of drug}}{\text{Theoretical amount ofdrug}} \times 100$$

Viscosity Measurements

Stability is significantly influenced by the rheological characteristics. Determining the microemulsion zone and separating it from other regions is made easier by changes in the rheological properties. To monitor and regulate the flow characteristics and guarantee the quality of the final product and the efficiency of the manufacturing process, rheological characterisation is crucial. Choosing a dermatological formulation that will lead to clinical effectiveness is aided by it.The Brookfield digital viscometer (DV-E model) may be used to determine it. After the samples were placed within the sample holder used for the viscosity measurement, it was placed inside a flow jacket that was fixed to the viscometer. The viscosity of the preparation was measured using the samples adapter (spindle no. 2) rotating at the ideal speed. The whole speed range, from 10 rpm to 100 rpm, was measured in 30 seconds.

In vitro drug release study

ITR/VRC laden microemulsion was released in vitro using the dialysis technique. 200 millilitres of PBS with a pH of 7.4 was used as the diffusion medium. The test tube had a burette stand connected to one end and an egg membrane covering the other. Additionally, the arrangement is set up such that the egg membrane touches the beaker containing the phosphate buffer saline (pH 7.4) immediately. A magnetic stirrer was used to agitate a beaker containing 200 millilitres of PBS

pH 7.4 solution at 37°C±0.5°C at 120 revolutions per minute. The egg membrane-covered test tube contained the microemulsion mixture. The formulation came into direct contact with the phosphate buffer saline (pH 7.4) while the test tube was submerged in the diffusion medium. For 240 minutes (4 hours), the drug samples were periodically removed from the diffusion medium while maintaining sink conditions. used a Shimadzu® 1800 double beam UV visible spectrophotometer to analyse the material. A UV spectrophotometer was used to measure the drug concentration at λmax 236 nm for ITC [15].

Results and discussion

Itraconazole (ITC), the model medicine, is a yellowish white crystalline powder with a m.p. of 242-245ºC.The drug's solubility is 71.8 in distilled water, 11.31 in 0.1 N HCl, 73.24 in 0.1 N NaOH, 123.31 in ethanol, 95.4 in oleic acid, and 87.27 in PBS pH 6.5. The medication has a partition coefficient of 1.16 and is hygroscopic.

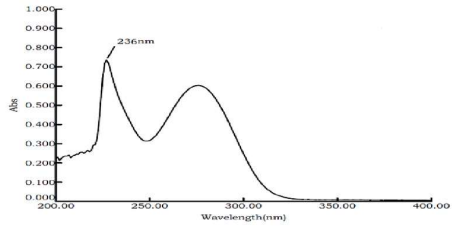

Figure 1: UV spectrum of ITC

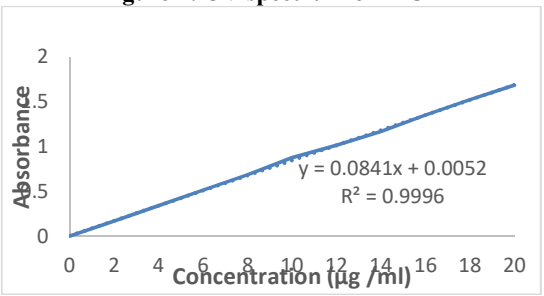

Figure 2: Standard curve of ITC in PBS (pH 7.4) 236 nm

Construction of pseudo-ternary phase diagrams

According to the early batch findings, batch code A groups that produce a clear solution after titrating with water and stay clear after diluting with water indicate the creation of a clear microemulsion; as a consequence, they are chosen for more evaluation research. After determining the proportion of each phase needed to generate the microemulsion, phase diagrams were created, and the medicated microemulsion was then created. Table 2 (oleic acid as oil phase) and Figure 3 show the pseudo-ternary phase diagrams with different weight ratios of Tween 80:ethanol.

Table 2: Preliminary batches of micro emulsion

S. No.	Batch code	Surfactant: Co-surfactant ratio	Observation
		(Tween 80: ethanol)	
1.	A	1:1	apparent

Table 3: Formulation of micro emulsion (A) Tween 80: Ethanol (1:1)

A (1:1)	Smix : oil		Water (ml)	Oil %	Smix %	Water %
A1	9: 1		5	6.56	60	33.23
A2	8:2		4	14.28	47.24	38.67
A3	7:3		2	20.42	58.23	14.38
A4	6:4		0.3	38.84	58.35	2.71
A5	5:5		0.2	49.01	49.21	1.96
A6	4:6		0.3	59.25	38.43	2.81
A7	3:7		0.1	69.40	29.02	0.89
A8	2:8		0.07	79.54	19.46	0.79
A9	1:9		0.04	86.43	9.51	0.308

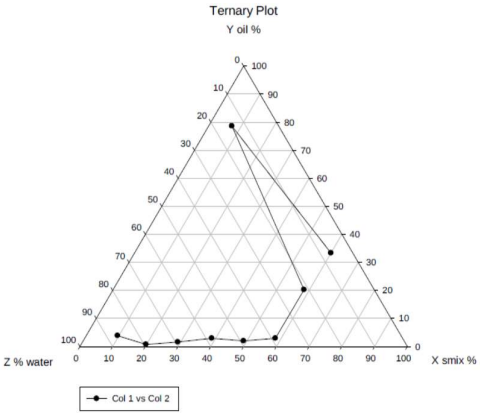

Figure 3: Ternary stage diagram of surfactant (Tween 80)/co-surfactant (ethanol) 1:1 ratio and oil (oleic acid)

Table 4: Composition of ITC loaded micro emulsion

S. No.	Materials	Quantity
1.	Drug Voriconazole	50 mg
2.	Oleic acid	6 ml
3.	Span 80	2ml
4.	Methanol	2ml
5.	Water	q. s.

Table 5: Description of micro emulsion (A6)

S. No.	Parameters	Results
1.	Visual observation	Clear
2.	%Transmittance value	98.20 %
3.	pH	5.3-6.5
4.	Drug content	92.5 %
5.	Viscosity (cps)	2221 ± 13.11 cps

The amount of surfactants in the microemulsion had a major impact on the drug's penetration rate. It

is evident from the permeation experiments that as the concentration of the oil and the combination of surfactant and co-surfactant decreases, the rate of permeation rises. The drug's increased thermodynamic activity in the microemulsion might be the cause of this.

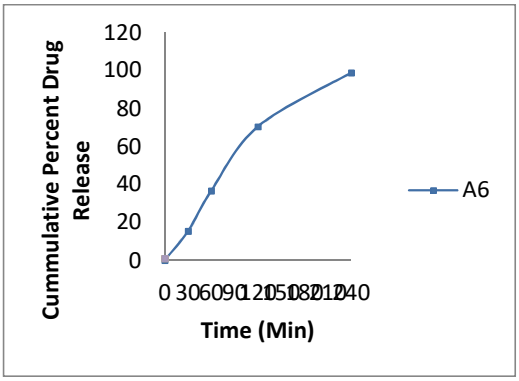

Figure 4: In vitro drug release study from prepared microemulsion (Zero-order drug release study)

Summary and Conclusion

The avoidance of hepatic first-pass metabolism, drug breakdown in the stomach, and associated toxicity effects, as well as the ease of administration and excellent control over drug delivery rate, are some of the benefits of topical drug administration over other approaches. Both lipophilic and hydrophilic active pharmacological agents are more readily absorbed via the skin when applied topically. To improve permeation, many strategies have been used, such as altering the characteristics of the medication, the vehicle, or the skin.The skin is immediately treated using topical medicines. Itraconazole microemulsion formulations were created for topical use. Because the formulation is in the nano range, the drug's penetrability may be improved. The formulation has encouraging qualities for topical medication delivery development and usage. These formulations may be very beneficial for medications that have a lower skin penetration rate since they are simple to manufacture and produce.

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