ORIGINAL ARTICLE

Formulation and Evaluation of Itraconazole Emulgel for Various Fungal Infections

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Abstract

Introduction: In the past few decades, there has been an exponential growth in the field of herbal medicine and excipients. The aim of the present research work was to investigate the potential of emulgel in enhancing the topical delivery of itraconazole using natural gelling agents. **Materials and Methods:** Emulgel formulations of itraconazole were formulated using two types of gelling agents, namely xanthan gum and guar gum. The influence of the type of the gelling agent and the concentration of both the oil phase and emulsifying agent on the drug release from the formulated emulgel was studied by preparing various batches. The prepared formulations were evaluated for their physical appearance, viscosity, drug release, globule size, skin irritation test, antifungal activity, and stability. Itraconazole cream available in market was used for comparison with prepared formulations. **Results and Discussion:** All the prepared emulgels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability, and pH value. The result of studied revealed that the optimized batch shows 96.04% release in 5 h.

Key words: Emulgel, guar gum, itraconazole, topical drug delivery, xanthan gum

INTRODUCTION

Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and better vehicle for hydrophobic or poorly water-soluble drugs.[1] They have a high patient acceptability since they possess the advantages of topical drug delivery and antifungal activity of both emulsions and gels. Direct (oil in water) systems are used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse (water in oil) systems.[2] Therefore, they have been recently used as vehicles to deliver various hydrophobic drugs to the skin.

Itraconazole is effective against several fungal strains such as *Candida albicans* and *Candida tropicalis*, which are responsible for topical candidiasis in >25% of patients suffering from this condition. Candida-related fungal infection is a common skin disease affecting two-thirds of all persons at least once during their lifetime.[3]

Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulation involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed.[4,5]

Itraconazole is a synthetic antifungal agent of the imidazole class; it works by slowing the growth of fungi that cause infection. It is used to treat fungal infection. Triazole drug targets the fungal-specific synthesis of membrane lipids. Itraconazole inserts preferentially into fungal membranes

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and disrupts their function. 5-fluorocytosine targets fungal-specific DNA replication.[6]

MATERIALS AND METHODS[7-11]

Itraconazole was procured from Cipla Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade and were used without any further chemical modification.

Preparation of Itraconazole Emulgel

Different formulations were prepared using various gelling agent and penetration enhancer Table 1. The method only differed in the process of making gel in different formulations. The preparation of emulsion was same in all the formulations. The gel formulations were prepared by dispersing xanthan gum and guar gum in purified water with constant stirring at a moderate speed. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Preservatives were dissolved in propylene glycol, whereas drug (Itraconazole) was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70°–80°C; then, the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

Evaluation of Emulgel[12-17]

Physical examination

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, grittiness, and phase separation.

Measurement of pH

pH is one of the most important parameters involved in the evaluation of emulgels. The pH values have an effect on the balance of the ionized and unionized form of the drug, and ionized and unionized forms of the drug would show different penetration behavior. The pH of all the formulations was evaluated using a pH meter and the pH was measured at room temperature.

Determination of viscosity

The viscosity of different Itraconazole emulgel formulations was determined at 25°C using a Brookfield viscometer.

Spreadability

Spreadability of the emulgel was determined 48 h after preparation of the emulgel using the wooden block and the glass slide apparatus. 1 g of the prepared emulgel was placed between two 10 cm × 10 cm glass plates (125 g each). A weight of 25 g was placed it in a pan and the time required for the upper glass plate to completely separate from the fixed glass plate was recorded. The spreadability was then calculated by the following formula:

$$S=M\times L/T$$

Where, S=Spreadability
L=Length of the glass plate used
M=Weight tied to the upper slide
T=Time taken to separate slide completely from each other.

Spreadability was measured in terms of g.cm/sec.

Extrudability

The method adopted for evaluating gel formulation for extrudability was based on the quantity in percentage of gel extruded from aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 s. More quantity extruded better was extrudability. The measurement of the extrudability of each formulation was in triplicate and the average values were presented. The extrudability was then calculated using the following formula:

Extrudability=Applied weight to extrude gel from tube (in gm)/Area (in cm^2).

Drug Content Determination

Drug content of formulations was measured by ultraviolet (UV) spectrophotometer. 1 ml of emulsion was diluted to 20 ml with methanol and volume was made up to 100 ml using phosphate buffer 7.4. A volume of 2 ml of this solution was further diluted to make 10 µg/ml solution of Itraconazole.

Table 1: Composition of different formulation batches (%w/w)

Ingredients	MIC	F1	F2	F3	F4
Itraconazole	-	1	1	1	1
Xanthan gum	-	0.75	1	-	-
Guar gum	-	-	-	0.75	1
Liquid paraffin	-	5	5	5	5
Span 20	-	1	1	1	1
Tween 20	-	0.5	0.5	0.5	0.5
Propylene glycol	-	5	5	5	5
Ethanol	-	2.5	2.5	2.5	2.5
Methyl paraben	-	0.1	0.1	0.1	0.1
Propyl paraben	-	0.05	0.05	0.05	0.05
Water	-	Q.S.	Q.S.	Q.S.	Q.S.

MIC: Marketed Itraconazole cream

Table 2: Physical examination

Formulation code	Color	Phase separation	Grittiness	Homogeneity	Consistency
F1	Off-white	No phase separation	–	+++	+++
F2	Off-white	No phase separation	–	+++	+++
F3	White	No phase separation	–	+++	+++
F4	White	No phase separation	–	+++	+++

Table 3: pH, viscosity, spreadability, extrudability, and drug content

Formulation code	pH	Viscosity (cps×10^3)	Spreadability	Extrudability	Drug content
MIC	6.21	91	+++	+++	99.28±0.83
F1	5.98	92	+++	+++	99.04±1.66
F2	6.21	94	+++	++	97.90±0.26
F3	6.29	97	++	++	96.69±2.38
F4	6.48	99	++	++	95.21±0.88

MIC: Marketed Itraconazole cream

Table 4: Skin irritation test

Formulation code	Skin irritation
F1	A
F2	A
F3	A
F4	A

A: No reaction, B: Slight erythema, C: Moderate erythema

Table 5: Stability studies F1 formulation

Parameters	Period of studies in months	
	0 month	3rd month
Drug content	99.04±1.66	98.66±0.03
pH	5.98	5.98
Homogeneity	+++Homogeneous	+++Homogeneous
Physical appearance	Off-white	Off-white

IN VITRO DRUG RELEASE STUDY

The *in vitro* drug release studies of the formulated emulgel were carried out in modified diffusion cell using dialysis membrane. The membrane was soaked in phosphate buffer solution (PBS) pH 7.4 for 9–12 h was to clamped carefully to one end of the hollow glass tube of dialysis cell. Then, emulgel (300 mg) was spread uniformly on the dialysis membrane. 100 ml of PBS pH 7.4 used as dissolution media was added to receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37±0.5°C. Sample (10 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrometrically at 273 nm and the cumulative percentage drug release was calculated.

Skin Irritation Test

Guinea pigs (400–500 g) of each sex were used for testing of skin irritation study. The animals were maintained on standard animal feed and had free across to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 cm^2 was marked on both the sides, one side served as control while the other sides were tested. Formulated emulgel was applied (500 mg/guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any Table 4.

Stability Studies

Stability study was performed. The most satisfactory emulgel formulation was kept at 37 ± 2°C and 60 ± 2°C. At the end of 1 month, the samples were analyzed for the physical properties, homogeneity, pH, and drug content Table 5.

RESULTS AND DISCUSSION

All prepared Itraconazole emulgel formulations were found off-white, white in color, and homogeneous with viscous consistency. Results are shown in Table 2. pH is measured with the help of pH meter and is in between 5.98 and 6.48. Viscosity of all prepared emulgel formulations was found in 91–99 (cps × 10^3). Spreadability: Spreadability of all emulgel formulations was measured with parallel glass slide method; it was found satisfactory. Grading is shown in Table 3. Extrudability was measured by suitable method and grading shown in Table 3. Drug content in emulgel formulations of Itraconazole was measured by UV spectrophotometer. The results are shown in Table 3. *In vitro* drug release study was performed in Franz diffusion cell for 5 h. Highest drug release found in F1 (96.04 ± 1.66) formulation and lowest in F4 (80.21 ± 0.88). Graph of percentage drug release versus

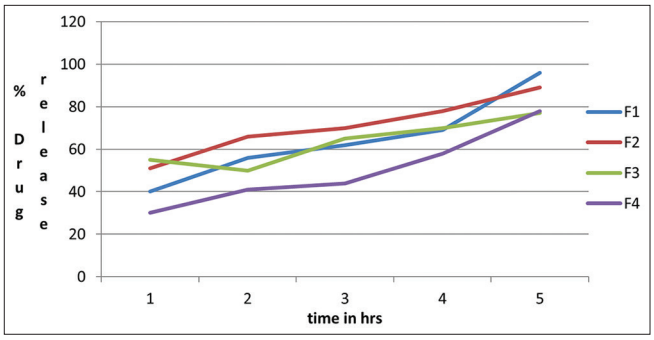

Figure 1: Graph of percentage drug release versus time in hours

time in hours shown in Figure 1. Skin irritation study was performed for all emulgel formulations and all formulations have not shown any irritation or edema. Stability studies performed as per ICH guidelines. All formulations evaluated for pH, physical appearance, and drug content after 3 months and there was no change in these values. Hence, it can be concluded that emulgel formulations were stable.

CONCLUSION

It can be concluded from the above results and discussion that Itraconazole emulgel formulations prepared with xanthan gum and guar gum showed acceptable physical properties. The optimized batch F1 of emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level proved to be the formula of choice since it showed the highest drug release in both types of gelling agent. As compared to marketed Itraconazole cream formulation FI, xanthan gum-based formulations showed more promising results of spreadability, extrudability, drug content, and for drug release. Hence, at last, it can be concluded that liquid paraffin-based Itraconazole emulgel with 0.75% concentration of natural gelling agent is promising topical therapy for various fungal infections.

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