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Original Research Article

FORMULATION AND DEVELOPMENT OF EMULGEL FOR TOPICAL DELIVERY OF ISOCONAZOLE TO TREAT FUNGAL DISEASES

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ABSTRACT

Fungal illnesses require more attention than ever before, considering the growing population of immunocompromised people who are more vulnerable to these diseases. Topical drug delivery systems have been used for centuries to treat local skin ailments. One such delivery system is emulgel. Emulgel, is being employed to successfully include a hydrophobic medicinal moiety while enjoying the distinctive properties of gels. Also, the emulgels are emollient, nonstaining, high shelf life, bio-friendly, translucent, and attractive appearance. Thus, this study aims at formulation & evaluation of emulgel of Isoconazole for treating fungal disease. The preparation & evaluation of emulgel was performed as per standard protocol. Results showed that all the six formulation had good washability, absence of clogging & good homogeneity. The colour of all the formulation was white cream. The Extrudability ranged from excellent to average. The spread ability extent was observed from minimum of 10.32 for F3 & maximum of 13.36 for F4. The maximum viscosity was observed for F4 which was 3265±14 cps. While the minimum viscosity was noted for F3 which was 3115±11 cps. The pH of all the formulation were close to the pH of skin hence acceptable. Further % drug content studies indicated that formulation F3 have maximum drug content of 99.12±0.25 %. The % Cumulative drug release of formulation F1-F6 data, point towards fact that, within 4 hours the maximum drug release was observed in case of F3 formulation. Also, The In vitro drug release data for optimized formulation F3 proved that this is most suitable formulation which can be used to treat fungal infection. Thus, it can be summarized that Isoconazole emulgel, being hydrophobic in nature and can be considered as a potential topical alternative for the treatment of skin infections and attaining controlled release with higher bioavailability and for drug delivery.

Keywords: Fungal infections, Skin infections, Isoconazole, Topical drug delivery, Emulgel

INTRODUCTION

Fungi are a diverse group of microorganisms that can be found in the environment, are part of the normal flora of humans and animals, and can cause moderate superficial infections to life-threatening invasive infections. Social and political communities ignore fungal infections. However, they afflict over a billion people each year, resulting in over 115 million life-threatening infections and over 15 million fatalities. Over the last 20 years, there have been huge advances in fungal diagnoses and antifungal drug development, yet the majority of the world's population has yet to profit from these advances.

Animals can get a variety of fungal illnesses, and some of these can be passed on to humans. Fungi affects those with low immunity. Yeasts, moulds, and some fungi that can exist as both a mould and a yeast cause fungal infections. They arise when they are breathed in, come into touch with skin, or enter the body by a cut, wound, or injections (Enoch *et al*., 2006; Richardson, 2005; Gullo, 2009).

The attempt to cure diseases has fueled the development of new medications, drugs, and delivery systems. Topical drug delivery systems have been used for centuries to treat local skin ailments. It is a localized drug delivery method that can be employed anywhere in the body via ophthalmic, rectal, vaginal, and dermal routes. Clinical evidence indicates that topical gel is a safe and effective therapy choice for the management of skin-related diseases, and it is utilized for local action to reduce the adverse effects associated with other conventional dosage forms. Topical drug delivery systems comprise a wide range of pharmaceutical dosage forms such as semisolids, liquid preparations, sprays, and solid powders. Gels, creams, and ointments are the most often used semisolid preparations for topical medication delivery (Jeong *et al*., 2021; Patil *et al*., 2019).

Emulsion-gels began to gain popularity in pharmaceutical topical semisolid dosage forms in the mid-1980s. Emulgel is an oil-in-water or water-in-oil emulsion that has been gelled by combining with a gelling agent. The use of transparent gels in cosmetics and pharmaceutical preparations has grown significantly within the principal group of semisolid preparations.

Despite the many advantages of gels and emulsions, one important drawback is their inability to distribute hydrophobic medicines and their instability during storage. To circumvent these restrictions, an emulsion-based technique, i.e., Emulgel, is being employed to successfully include a hydrophobic medicinal moiety while enjoying the distinctive properties of gels. Emulgel serves as a dual control because it is both an emulsion and a gel (Talat *et al.*, 2021; Lakshmi *et al*., 2021). Thus, this study aims at formulation & evaluation of emulgel of Isoconazole for treating fungal disease.

MATERIALS AND METHODS

Chemical and reagent

Carbapol, Liquid paraffin, Tween Span 20, Propylene glycol, Ethanol, Methyl parabene, Ethyl parabene, Clove oil, Mentha oil & Water were obtained from S.D fine chemicals Mumbai. All chemicals used were of analytical grade. All solvents and reagents were of analytical grade.

Formulation development of emulsion

Preparation of emulsion

The general method was employed for preparation of an emulsion was as follows: The oil phase was prepared by dissolving Span 20 in liquid paraffin in the different ration given in table 6.1 while the aqueous phase was prepared by dissolving Tween 20 in purified water (Vats *et al.,* 2014). 1 gram of Isoconazole was dissolved in 5 ml of ethanol, while 0.15 g of methylparaben and 0.05 g of propylparaben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase. Both the oily and aqueous phases were separately heated to 70-80°C.

Then, the oil phase was added to the aqueous phase with continuous stirring at 500 rpm until cooled to room temperature.

Preparation of carbopol gel

Fifty (50) grams of the carbopol gel was prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6.5-6.8 using 0.5 N of sodium hydroxide (Kute and Saudagar, 2013).

Formulation of Isoconazole emulgel

Six formulations of Isoconazole were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel as shown in table 1.

Evaluation of emulgel

Physical characteristic

The physical characteristic was checked for emulgel formulations (colour, clogging, homogeneity and texture) and observations were noted (Asija *et al.*, 2015).

Determination of pH

The pH of the emulgel was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were noted (Singla *et al.*, 2012).

Extrudability study

The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability

Method:

Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50 with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted.

Viscosity

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer (Shehata *et al*., 2020). The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should

sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature ($25\pm/1^0C$) before the measurements.

Drug content

1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 272 nm. Drug content was calculated by linear regression analysis of the calibration curve.

***In-vitro* drug release studies using the prehydrated cellophane membrane**

Diffusion Studies:

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of upto 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 272 nm using neutralizing 7.4 pH phosphate buffer as blank.

Table 1: Different formulations of Isoconazole emulgel (% w/w)

Formulation	Isoconazole (mg)	Carbomer 941	Liquid paraffin	Span 20	Tween 20	Propylene glycol	water
F1	500	0.5	5	2	5	5	100
F2	500	0.5	5	2	10	5	100
F3	500	1.0	10	4	5	5	100
F4	500	1.0	10	4	10	5	100
F5	500	1.5	5	2	5	5	100
F6	500	1.5	5	2	10	5	100

Table 2: Psychorheological characteristic

Formulation	Washability	Observation	Clogging	Homogeneity
F1	+++	white cream	Absent	Good
F2	+++	white cream	Absent	Good
F3	+++	white cream	Absent	Good
F4	+++	white cream	Absent	Good
F5	+++	white cream	Present	Average
F6	+++	white cream	Present	Average

Washability - Excellent: +++, Good: ++, Average: +, Poor: -

Table 3: Extrudability and Spreadability study

Formulation	Extrudability	Spreadability (gcm/sec)
F1	++	12.25
F2	++	11.15
F3	+++	10.32
F4	+++	13.36
F5	+	12.25
F6	+	11.45

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4: Viscosity and pH

Formulation	Viscosity (cps)	pH
F1	3325±15	6.85±0.04
F2	3245±12	6.74±0.02
F3	3115±11	6.72±0.03
F4	3265±14	6.65±0.05
F5	3125±16	6.55±0.02
F6	3045±14	6.71±0.06

* Average of three determinations

Table 5: Results of drug content of emulgel

Formulation	% Drug content
F1	97.56±0.21
F2	98.85±0.32
F3	99.12±0.25
F4	98.74±0.26
F5	98.65±0.21
F6	98.12±0.14

Table 6: % Cumulative drug release of formulation F1-F6

S. No.	Time (min)	% Cumulative drug release						Marketed Formulation
		F1	F2	F3	F4	F5	F6	
1	15	22.25	26.65	29.95	26.65	24.48	21.45	35.65
2	30	32.25	36.52	39.98	35.45	32.25	35.58	45.58
3	45	45.58	48.87	52.26	39.98	39.98	46.65	96.65
4	60	59.98	59.95	68.85	57.74	56.65	59.98	-
5	120	66.98	66.85	85.54	82.26	73.32	66.58	-
6	240	78.85	83.32	99.05	89.98	85.45	78.85	-

Table 7: *In vitro* drug release data for optimized formulation F3

S. No.	Time (min)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	15	3.873	0.588	29.95	1.426	73.35	1.865
2	30	5.477	0.739	39.98	1.602	60.02	1.778
3	45	6.708	0.827	52.26	1.689	51.16	1.709
4	60	7.746	0.889	68.85	1.793	37.88	1.578
5	120	10.954	1.04	85.54	1.897	21.15	1.325
6	240	15.492	1.19	99.05	1.995	1.16	0.064

* Average of three determinations

RESULTS AND DISCUSSION

In case of emulgel, six different formulations were made by changing the amount of various ingredients. It was observed that all the six formulation had good washability, absence of clogging & good homogeneity. The colour of all the formulation was white cream. The Extrudability ranged from excellent to average. The spreadability extent was observed from minimum of 10.32 for F3 & maximum of 13.36 for F4. The pattern of Spreadibility can be arranged in increasing order as F3<F2<F6 < FI=F5<F4.

The viscosity & pH of formulation was also analysed. The maximum viscosity was observed for F4 which was 3265±14 cps. While the minimum viscosity was noted for F3 which was 3115±11 cps. The pH of all the formulation were close to the pH of skin hence acceptable. Further % drug content studies indicated that formulation F3 have maximum drug content of 99.12±0.25 %. The % Cumulative drug release of formulation F1-F6 data point towards fact that, within 4 hours the maximum drug release was observed in case of F3 formulation. The drug release from the emulgel formulation was found to be particularly persistent and regulated. The r2 value obtained for the first order release kinetics (0.989) is higher than that for the zero order release kinetics (0.827). A higher r2 value suggests a better fit of the data to the first order release kinetic model compared to the zero order model. Also, The *in vitro* drug release data for optimized formulation F3 proved that this is most suitable formulation which can be used to treat fungal infection.

CONCLUSION

Based on the results of the experiments, it is concluded that the nature of the polymers used in the creation of gels, as well as their concentrations, had an effect on the release of Isoconazole from the emulgel base. The emulgel formulations developed demonstrated acceptable physiochemical parameters as well as the best viscosity and spreadability. In any of the formulations, there was no swelling, syneresis, or phase separation. The F3 emulgel demonstrated the highest drug release. Isoconazole emulgel, being hydrophobic in nature and can be considered as a potential topical alternative for the treatment of skin infections and attaining controlled release with higher bioavailability and for drug delivery.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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