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

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Abstract

Fungal infections have become a pressing concern, especially given the increasing population of immunocompromised individuals who are more susceptible to such diseases. Traditional topical drug delivery systems have a long history in treating localized skin ailments, and one such system gaining prominence is the emulgel. Emulgels offer the advantage of successfully incorporating hydrophobic medicinal components while harnessing the unique properties of gels. These formulations are emollient, non-staining, possess a high shelf life, are environmentally friendly, exhibit translucency, and boast an attractive appearance. Consequently, this study aims to formulate and evaluate an emulgel containing Isoconazole for the treatment of fungal diseases. The preparation and evaluation of the emulgel were conducted following standard protocols. The results demonstrated that all six formulations exhibited good washability, an absence of clogging, and homogeneity. The color of each formulation resembled a white cream, and extrudability ranged from excellent to average. Spreadability ranged from a minimum of 10.32 for F3 to a maximum of 13.36 for F4. The highest viscosity was observed for F4 at 3265±14 cps, while the lowest viscosity was noted for F3 at 3115±11 cps. The pH of all formulations closely matched the skin's pH, making them acceptable for topical application. Moreover, % drug content studies revealed that formulation F3 had the highest drug content at 99.12±0.25%. Analyzing the % cumulative drug release of formulations F1-F6, it became evident that F3 achieved the maximum drug release within 4 hours. In vitro drug release data for the optimized formulation, F3, further confirmed its suitability for treating fungal infections. Therefore, it can be concluded that Isoconazole emulgel, with its hydrophobic nature, represents a potential topical alternative for the effective treatment of skin infections. The controlled release of the drug enhances bioavailability, making this emulgel a promising avenue for drug delivery in the context of fungal illnesses.

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

Introduction

Fungi constitute a diverse group of microorganisms prevalent in the environment, forming a natural part of the flora in humans and animals. They have the potential to cause superficial infections ranging from moderate to life-threatening invasive conditions. Despite their impact on over a billion individuals annually, resulting in more than 115 million life-threatening infections and over 15 million fatalities, fungal infections tend to be overlooked by social and political communities. In the past two decades, significant strides have been made in the diagnosis of fungal infections and the development of antifungal drugs. However, a considerable portion of the global population has yet to benefit from these advancements. Various fungal illnesses affecting animals can also be transmitted to humans, particularly those with compromised immune systems. Fungal infections are caused by yeasts, molds, and certain fungi that can exist in both mold and yeast forms. Transmission occurs through inhalation, skin contact, or entry into the body through cuts, wounds, or injections (Enoch et al., 2006; Richardson, 2005; Gullo, 2009).

The quest to combat diseases has driven the innovation of new medications, drugs, and delivery systems. Topical drug delivery systems, employed for centuries to address localized skin ailments, offer a localized approach applicable to various body parts through ophthalmic, rectal, vaginal, and dermal routes. Clinical evidence supports the use of topical gel as a safe and effective therapy for managing skin-related diseases, providing local action to mitigate adverse effects associated with conventional dosage forms. Topical drug delivery systems encompass a diverse array of pharmaceutical forms, including semisolids, liquid preparations, sprays, and solid powders. Among these, gels, creams, and ointments are the most frequently used semisolid preparations for topical medication delivery (Jeong et al., 2021; Patil et al., 2019).

Emulsion-gels gained popularity in pharmaceutical topical semisolid dosage forms in the mid-1980s. Emulgel, an oil-in-water or water-in-oil emulsion gelled with the addition of a gelling agent, emerged as a transparent gel option in cosmetics and pharmaceutical preparations. Despite the many advantages of gels and emulsions, their limitation in distributing hydrophobic medicines and susceptibility to instability during storage pose challenges. To overcome these constraints, an emulsion-based technique,

namely Emulgel, is employed to successfully incorporate a hydrophobic medicinal component while leveraging the distinctive properties of gels. Emulgel serves as a dual-control system, functioning as both an emulsion and a gel (Talat et al., 2021; Lakshmi et al., 2021). Hence, this study aims to formulate and evaluate an emulgel containing Isoconazole for the treatment of fungal diseases.

Materials & Methods

Chemicals and Reagents: Carbopol, Liquid paraffin, Tween Span 20, Propylene glycol, Ethanol, Methyl paraben, Ethyl paraben, Clove oil, Mentha oil, and Water were sourced from S.D fine chemicals, Mumbai. All chemicals utilized adhered to analytical grade standards.

Formulation Development of Emulsion:

Preparation of Emulsion: The general method employed for emulsion preparation involved dissolving Span 20 in liquid paraffin in varying ratios (refer to Table 6.1) for the oil phase, while the aqueous phase was created by dissolving Tween 20 in purified water (Vats et al., 2014). Isoconazole (1 gram) was dissolved in 5 ml of ethanol, and methylparaben (0.15 g) and propylparaben (0.05 g) were dissolved in 5 gm of propylene glycol. The latter mixture was combined with the aqueous phase. Both the oil and aqueous phases were individually heated to 70-80°C. Subsequently, 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 grams of carbopol gel were prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with the aid of a moderate-speed stirrer (50 rpm). The pH was then adjusted to 6.5-6.8 using 0.5 N sodium hydroxide (Kute and Saudagar, 2013).

Formulation of Isoconazole Emulgel: Six formulations of Isoconazole were developed by dispersing the obtained emulsions with the gel in a 1:1 ratio, achieving a homogeneous emulgel (see Table 1).

Evaluation of Emulgel

Physical Characteristics: The physical characteristics of the emulgel formulations, including color, clogging, homogeneity, and texture, were assessed and recorded (Asija et al., 2015).

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

Determination of pH: The pH of the emulgel was determined using a digital pH meter. One gram of gel was dissolved in 25 ml of distilled water, and the electrode was immersed in the gel formulation for 30 minutes until a constant reading was obtained. The pH readings for each formulation were replicated two times.

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

Extrudability Study: Emulgel formulations were filled into collapsible metal or aluminum tubes. The tubes were pressed to extrude the material, and the extrudability of the formulation was assessed.

Spreadability: *Method:* Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation to be assessed for spreadability was placed on one slide. The second slide was positioned over the emulgel, forming a sandwich, and a weight of 100 grams was placed on the upper slide. This process created a uniform thin layer of the emulgel between the two slides. After removing excess emulgel, the time taken for the upper slide to travel 6 cm and separate from the lower slide under the weight was recorded.

Viscosity: The viscosity of the prepared gel was measured using a Brookfield digital viscometer (Shehata et al., 2020). Viscosity was measured with spindle no. 6 at 10 rpm

and 25°C. The gel was allowed to settle for 30 minutes at a constant temperature before measurements.

Drug Content: One gram of the prepared gel was mixed with 100 ml of ethanol. Aliquots of different concentrations were prepared through suitable dilutions after filtering the stock solution, and absorbance was measured at 272 nm. Drug content was calculated using linear regression analysis of the calibration curve.

In-Vitro Drug Release Studies Using Prehydrated Cellophane Membrane:

Diffusion Studies: In-vitro diffusion of the drug from different gel preparations was studied using a standard cylindrical tube fabricated in the laboratory. The diffusion cell membrane, applied with 1 gram of the formulation, was tied to one end of the tube, with the other end open to ambient conditions acting as the donor compartment. Aliquots were withdrawn periodically at predetermined intervals, up to 12 hours, and replaced by an equal volume of the receptor medium. The aliquots were diluted and analyzed by UV-Vis spectrophotometer at 272 nm.

Results & Discussion: Six different emulgel formulations were prepared with varying ingredient amounts. All six formulations exhibited good washability, absence of clogging, and homogeneity. The color of all formulations was a white cream. Extrudability ranged from excellent to average, and spreadability varied from a minimum of 10.32 for F3 to a maximum of 13.36 for F4. Viscosity and pH were analyzed, with F4 having the maximum viscosity (3265±14 cps) and F3 having the minimum viscosity (3115±11 cps). The pH of all formulations was close to the pH of the skin, indicating acceptability. Drug content studies revealed that formulation F3 had the maximum drug content (99.12±0.25%). Cumulative drug release data for formulations F1-F6 indicated that F3 achieved the maximum drug release within 4 hours. The release from the emulgel formulation was persistent and regulated, as evidenced by the in-vitro drug release studies. The optimized formulation F3 proved to be the most suitable for treating fungal infections, demonstrating persistent and controlled drug release kinetics.

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 ormulation
		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

Conclusion

The outcomes of the conducted experiments provide compelling evidence that the selection and concentration of polymers used in gel formation significantly impacted the release of Isoconazole from the emulgel base. The formulated emulgel preparations exhibited favorable physiochemical characteristics, including optimal viscosity and spreadability. Notably, none of the formulations displayed issues such as swelling, syneresis, or phase separation.

Among the various formulations, F3emulgel emerged as the standout performer, demonstrating the highest drug release profile. This underscores the crucial role of formulation parameters in achieving targeted drug release kinetics. The hydrophobic nature of Isoconazole in the emulgel context positions it as a promising topical alternative for effectively treating skin infections. Furthermore, the emulgel platform allows for controlled drug release, contributing to enhanced bioavailability and an effective drug delivery mechanism.

In summary, the developed Isoconazole emulgel, with its favorable attributes and superior drug release characteristics, holds substantial promise as a topical solution for the treatment of skin infections. The controlled release mechanism and improved bioavailability further underscore its potential as a valuable addition to dermatological therapeutics.

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