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Original Research Article

FORMULATION & EVALUATION OF TOLNAFTATE LOADED INVASOMAL GEL

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ABSTRACT

The growing number of immunosuppressed individuals who are at increased risk for developing fungi illnesses, fungi diseases need more attention than ever before. Transdermal drug delivery is the term for the method of administering medication through the skin to achieve a local or systemic treatment that has been given clinical approval. Invasomes are a new type of vesicle penetration-enhancing capabilities, boosting or improving medication absorption via the skin. Thus, this study aims at formulation & evaluation of Tolnaftate loaded Invasomal gel. The formulation & evaluation of gel was done by standard parameters. Results showed that the highest % entrapment efficiency was recorded for F4 formulation which is 72.32±0.18. Also, the average vesicle size for F4 was noticed to be 215.65±0.22nm. The zeta potential for F4 was seen to be -38.45mV. Further three formulation of ivasomal gel was made & evaluated for various parameters. The maximum % of drug content was observed for IG2 gel formulation as 99.45±0.23. The Extrudability (g) & Spreadibility (g.cm/sec) was observed to be 145±4 & 10.26±0.32 while Viscosity (cps) & pH was observed to be 3365±11 & 6.78±0.25. The In vitro drug release study pattern for IG 2 indicate that the drug release at 12 hour was 99.15±0.21. The highest R2 value was found to be 0.986, so the reaction found to follow the higuchi kinetics.The result of stability studies indicates that the formulated invasomal gel is stable for maximum 2 months as after that the drug content was observed to be reduced. From results it can be concluded that the formed invasomal gel of Tolnaftate may be useful to treat fungal skin infections.

Keywords: Fungal infections, Invasome, Transdermal drug delivery, Tolnaftate, Invasomal gel.

INTRODUCTION:

Fungal infections are becoming more common at an alarming rate, placing immense strain on medical personnel to diagnose and treat them. A large amount of morbidity and mortality is also caused by newly emerging fungal infections. This emergence is directly linked to the rise in the number of immunocompromised people in society. Granulocytopenia, advanced HIV infection, bone marrow and solid organ transplantation, cancer, diabetes mellitus, severe burn and trauma, and severe malnutrition are only a few of the conditions that make a person more susceptible to having low immunity.

A few elements that encourage these emergences include demographic changes, microbial adaptation, and technological advancements (Enoch *et al*., 2006; Wheat *et al*., 2002).

Transdermal drug delivery is the term for the method of administering medication through the skin to achieve a local or systemic treatment that has been given clinical approval. After oral administration and injection, it is the third most common method of medication delivery. The convenience of the transdermal route of drug administration and its potential to decrease blood drug fluctuation and hazardous side effects are its benefits. Additionally, the medication may avoid the liver's first-pass side effect to avoid being metabolized in the digestive system. Invasomes are a new type of vesicle that contain terpenes and aid to improve skin penetration when compared to traditional liposomes. They are unique (owing to their improved drug efficacy, boosting patient compliance, and comfort) soft, elastic liposomal vesicles with high membrane fluidity that contain terpene and ethanol that act as penetration enhancers. These vesicles are possible carriers for terpenes that have penetration-enhancing capabilities, boosting or improving medication absorption via the skin (Mishra and Bonde, 2020; Benson, 2005).

The term "Gel" was first used to describe various semisolid materials in the late 1800s based on their physiological properties rather than their molecular makeup. Gels are a cross-linked, highly diluted solution that, at steady state, has no flow. They are made up of a two-part, liquid-rich semisolid system. The continuous structure that gives them solid-like qualities is their defining attribute. Due to its biocompatibility, network structure, and molecular stability of the integrated bioactive chemical, gels have emerged as a leading medium for drug delivery formulations (Rathod and Mehta, 2015).

The topical medication tolnaftate is used to treat ringworm, jock itch, and other skin infections. Along with other antifungals, tolnaftate is also used to treat infections of the nails, scalp, palms, and soles of the feet. You can use the powder and powder aerosol to stop athlete's foot (Gire *et al*., 2018). Thus, this study aims at formulation & evaluation of Tolnaftate loaded Invasomal gel.

MATERIALS AND METHODS

Formulation optimization of Tolnaftate loaded Invasomes

Tolnaftate was loaded in to invasomes by mechanical dispersion technique. Soya Phosphatidylcholine (0.5 to 1% w/v) was added to ethanol and vortexed for 5 minutes (Dragicevic-Curic *et al.*, 2009; Dragicevic-Curic *et al.*, 2010). Drug and terpenes (0.5 to 1.5%) were added under constant vortexing, this mixture was sonicated for 5 minutes. Fine stream of Phosphate buffer saline (upto 10% w/v) was added with syringe under constant vortexing. It was vortexed for additional 5 minutes to obtain final invasomal preparation.

Preparation of gel base

Carbopol 934 (1-3% w/v) Invasome based gel formulation i.e. IG-1 of 1% w/v, IG-2 of 2% w/v, IG-3 of 3% w/v) was accurately weighed and dispersed into double distilled water (80ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then

10ml of propylene glycol was added to this solution (Badran *et al.,* 2009). The obtained slightly acidic solution was neutralized by drop wise addition of 0.05 N sodium hydroxide solutions, and again mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the gel base was adjusted to 6.5. The same procedure was used to formulate Invasomes containing gel in which previously prepared Invasomes suspension was added. Invasomes preparation corresponding to 1% w/w of drug was incorporated into the gel base to get the desired concentration of drug in gel base.

Evaluation of Tolnaftate loaded Invasomes
Entrapment efficiency

Entrapment efficiency of Tolnaftate Invasomes formulation was determined using centrifugation method (Haag *et al.,* 2011). The entrapment efficiency of acyclovir in invasomes vesicle was determined by ultracentrifugation, 10mL of invasomes formulation were collect in test tube. The amount of drug not entrapped in the invasomes was determined by centrifuging at 3,000 rpm and collect the supernatant, the supernatant layer was separated, diluted with water suitably and drug concentration was determined at 256 nm using UV spectrophotometer

Vesicle size

Microscopic analysis was performed to determine the average size of prepared invasomes (Dragicevic-Curic *et al.,* 2008). Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip. The prepared slide was examined under trinocular microscopic at 400 X. The diameters of more than 150 vesicles were randomly measured using calibrated ocular and stage micrometer.

Evaluation of Invasomes gel

Measurement of viscosity

Viscosity measurements of prepared topical Invasomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted (Dragicevic-Curic *et al.,* 2011).

Drug content

Accurately weighed equivalent to 100 mg of topical Invasomes gel was taken in beaker and added 20 ml of methanol (Ayman *et al.,* 2001). This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at λ_{max} 256 nm.

Extrudability study

Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load (Kalpana and

Lakshmi, 2013). More the quantity of gel extruded shows better extrudability. It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility

Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. It was determined by method reported by Multimer *et al.,* (1956). An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan.To determine spreadibility, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 10 cm upon adding 80 g of weight was noted.

***In-vitro* drug diffusion study**

The *in-vitro* diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion (Aqil *et al.,* 2007). The franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4.

The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32±0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength of 256 nm.

Table 1: Formulation optimization of Tolnaftate loaded Invasomes

Ingredient (%)	F1	F2	F3	F4	F5	F6
Tolnaftate (mg)	100	100	100	100	100	100
Phosphotidylcholine (%)	0.25	0.5	0.75	0.25	0.5	0.75
Terpenes (%)	0.25	0.25	0.50	0.50	0.75	0.75
Ethanol (ml)	10	10	10	10	10	10

Table 2: Formulation optimization of invasomes loaded gel

Ingredient (%)	IG-1	IG-2	IG-3
Drug (Invasomes equivalent to 1%)	1	1	1
Carbopol 934	1	2	3
Propylene glycol	0.2	0.2	0.2
Water (ml)	100	100	100

Table 3 Entrapment efficiency and average vesicle size

Formulation Code	% Entrapment efficiency	Average vesicle size (nm)
F1	67.85±0.25	285.65±0.22
F2	69.95±0.12	292.32±0.15
F3	64.65±0.22	278.85±0.32
F4	72.32±0.18	215.65±0.22
F5	68.12±0.14	236.65±0.16
F6	68.78±0.13	248.85±0.32

Table 4: Characterization of optimized formulation of invasomes

Formulation	Average vesicle size (nm)	% Entrapment efficiency	Zeta Potential (mV)
F-4	215.65 ± 0.25	72.32±0.18	-38.45

Table 5: Characterization of gel based formulation of Invasomes

Gel formulation	Viscosity (cps)	pH	Drug Content (%)	Extrudability (g)	Spreadibility (g.cm/sec)
IG-1	3458±12	6.32±0.15	98.85±0.15	156±5	11.45±0.25
IG-2	3365±11	6.78±0.25	99.45±0.23	145±4	10.26±0.32
IG-3	3215±10	6.65±0.32	97.45±0.14	136±7	9.78±0.15

Table 6: *In vitro* drug release study of prepared optimized gel formulation IG-2

S. No.	Time (hr)	% Cumulative Drug Release*
1	0.5	10.25±0.15
2	1	14.65±0.23
3	2	38.98±0.14
4	4	46.65±0.32
5	6	69.95±0.15
6	8	76.65±0.13
7	10	88.98±0.14
8	12	99.15±0.21

Table 7: *In-vitro* drug release data for optimized formulation IG-2

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	10.25	1.011	89.75	1.953
1	1	0	14.65	1.166	85.35	1.931
2	1.414	0.301	38.98	1.591	61.02	1.785
4	2	0.602	46.65	1.669	53.35	1.727
6	2.449	0.778	69.95	1.845	30.05	1.478
8	2.828	0.903	76.65	1.885	23.35	1.368
10	3.162	1	88.98	1.949	11.02	1.042
12	3.464	1.079	99.15	1.996	0.85	-0.071

Table 8: Regression analysis data of optimized gel formulation IG-2

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
IG-2	0.954	0.819	0.986	0.972

RESULTS AND DISCUSSION

The highest % entrapment efficiency was recorded for F4 formulation which is 72.32±0.18. Also, the average vesicle size for F4 was noticed to be 215.65±0.22nm. The zeta potential for F4 was seen to be 38.45mV. Further three formulation of invasomal gel was made & evaluated for various parameters. The maximum % of drug content was observed for IG2 gel formulation as 99.45±0.23. The extrudability (g) and spreadibility (g.cm/sec) was observed to be 145±4 & 10.26±0.32 while viscosity (cps) & pH was observed to be 3365±11 & 6.78±0.25. The *in vitro* drug release study pattern for IG 2 indicates that the drug release at 12 hr was 99.15±0.21. The highest R^2 value was found to be 0.986, so the reaction found to follow the higuchi kinetics. The result of stability studies indicate that the formulated invasomal gel is stable for maximum 2 months as after that the drug content was observed to be reduced.

CONCLUSION

The invasomes, which have the potential to be a useful tool for medication delivery via the skin and have superior skin permeability. Several chemical compounds and pharmaceutical active components are quite potent, yet their therapeutic activity is not as great. Because of their unique and adaptable qualities, invasomes are a novel carrier that can be used to target them. Invasomes made their triumphant entry into the field of pharmaceutical application. Since medication encapsulation, invadesomes have greatly improved the pharmacokinetic characteristics. Additionally, the penetration rate, the capacity to transfer the actives to the intended region, low toxicity, etc. All affects how effective the invasome dosage form is. Invasomal gel have higher penetration rate through the skin compared to liposomes and ethosomes. Invasomal gel provide a number of advantages including improving the drug efficacy, enhancing patient compliance and comfort. Enhanced delivery of drug through the skin and cellular membranes by means of an invasomal gel carrier opens numerous challenges and opportunities for research and future development of novel improved therapies for fungal diseases.

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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