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Der Pharmacia Lettre, 2011: 3 (5) 125-131
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0974-248X
USA CODEN: DPLEB4

Formulation and Evaluation of Fluconazole Amphiphilogel

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ABSTRACT

The studies were conducted with an object to develop stable safe and efficient delivery system for Antifungal drug fluconazole. During the course of studies different Amphiphilogel formulations of fluconazole for topical application were prepared by using sorbitan monostearate (span 60), Tweem 80 and Tween 20, Iso-propyl myristate, purified water. The formulated fluconazole were evaluated for psychorheological characteristic, drug content, pH, spreadability. The viscosity of different formulations were determined by using Brookfield Viscometer at 25°C, the viscosity of formulations increases as the surfactant concentration increases. In vitro release studies were carried out using franz diffusion cell at Phosphate buffer pH 7.4 at 50 rpm. The cumulative % drug releases iXSn the formulation were found to be 88.70- 96.48 %. Finally stability studies were carried out for one month's showed no separation of gel indicating overall stability. TLC studies clearly indicated thatY there is no any interaction in formulation.

Keywords: Amphiphilogel, Fluconazole, Span 60, Tween 80, Iso-propyl myristate.

INTRODUCTION

Fluconazole is chemically 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol, a synthetic triazole derivative antifungal agent that has been shown to be effective against a wide range of systemic and superficial fungal infections, following both oral and intravenous administration [1]. Fluconazole, a novel bis-triazole antifungal agent introduced in 1990, has systemic effects that may be beneficial for other fungal infections [2]. Subjects in the fluconazole prophylactic arm of one antifungal placebocontrolled trial showed improvement of dermatophytoses, such as tinea pedis, onychomycosis, and tinea cruris. In addition, systemic fluconazole prophylaxis may prevent esophageal and vaginal candidiasis, cryptococcemia, histoplasmosis, and other deep fungal infections[3]. Unlike ketoconazole, fluconazole is not altered by changes in gastric acidity and carries less risk of hepatotoxicity; however, many of the same drug interactions are possible. A newly raised concern about the wide spread use of fluconazole is the potential for development of azole-resistant Candida albicans and selection of nonalbicans Candida species, which also increase in prevalence with immune decline and further complicate management of some individuals [4,5].

Fungal infection of skin is now-a-days one of the common dermatological problem. The physicians have a wide choice for treatment from solid dosage forms to semisolid and to liquid formulations. For skin care and the topical treatment of dermatological disease, a wide choice of vehicles ranging from solids to semisolids and liquid preparations is available to clini-cians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceuticals. The effect of formulation additives on drug permeation through skin has been investigated in which the penetration rate of a topical agent may be influenced by drug—vehicle, drug—skin, and vehicle–skin interactions . In the clinical assessment of a topical agent, the vehicle may signifi-cantly affect drug release and skin penetration, thereby altering biological activity. widely accepted in both cosmetics and pharmaceuticals [6,7].

Amphiphilo gel is a semisolid system or being a compound (as a surfactant) consisting of molecules having a polar water-soluble group attached to a water-insoluble hydrocarbon chain. The amphiphilogels are also being studied as topical and transdermal carriers for drugs and vaccines; it was thought that the surfactant nature of the gels would enhance permeation of the active agents into and/or through the skin. The fact that the surfactants were nonionic indicated that the gels could be used as topical/ transdermal carriers without causing significant irritancy to the skin. Indeed, in experiments in mice and in man, we have shown that the gels, applied twice a day for 5 consecutive days, showed little irritancy to the skin [8].

The aim of the present research work is to formulate and evaluate amphiphilo gel of Antifungal drug: Fluconazole for topical drug delivery in pharmaceutical system to enhances the penetration efficacy of drug, Reduction in drug toxicity, Reduction in dosing frequency of drug. Such type of drug delivery systems is designed to deliver the drug in such a way that the drug level is maintained within the therapeutic window for a period as long as the system continues to deliver the drug and to avoid fluctuations in plasma drug level.

MATERIALS AND METHODS

Materials

Fluconazole was received from Glenmark generic ltd., Goa, Span 20, Tween 20, Tween 80, Iso-propyl meristate were purchased from S. K. Traders, Indore. All other chemicals/reagents used were of analytical grade.

Methods

In the formulation of amphiphilogel, Span 60 (sorbitan monostearate) were used as the gelators (solid component of the gel), and the fluid phases consisted of liquid Tweens 80/20. The solid gelator was weighed into a glass vial and the required amount of liquid surfactant was added. The vial was then heating at a 60°C for 10 min with continuous stirring. The solid gelator dissolved/dispersed in the liquid surfactant. To this mixture the oil phase comprising of IPM with continuous stirring on a magnetic stirrer. Drug was dissolved in a methanol and added to the sol gel. Water was added dropwisw with constant stirring to get a clear transparent and viscous sol gel. The sol phase was allowed to cool by standing at room temperature overnight to produced amphiphilogel. The compositions of amphiphilogel were show in Table 1.

Table 1. Formulation of Amphiphilogel

Ingredients	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
Fluconazole	1	1	1	1	1	1	1	1
Span 60	5	5	5	5	10	10	10	10
Tween 80	40	-	50	-	35	-	30	-
Tween 20	-	40	-	50	-	35	-	30
Isopropyl myristate	15	15	15	15	15	15	15	15
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Amphiphilogel:

a. Physical Characterization [9]: The formulated amphiphilogel were inspected visually for colour, presence of any clog and sudden viscosity changes. The formulations were applied on the skin and the feel was experienced psychorheologically.

b. Spreadability [10]: The parallel plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations.

Procedure: two glass slide of 20×20 cm were selected. The gel formulations whose Spreadibility had to be determined were placed over one of the slides. The other slide was placed upon the top of the gel such that the gel was sandwiched between the two slides in an area occupied by a distance of 60. cm along 100g weight was placed upon the upper slide so that the gel between the two slides was pressed uniformly to form a thin layer. The weight was removed and the excess of gels adhering to the slide was scrapped off. The two slides in positioned were fixed to a stand without slightest disturbance and in such a way that only the upper slide to slip off freely by the force of weight tied to it. A 20 g weight was tied to upper slide carefully. The time taken for the upper slide to travel the distance of 6 cm and separate away from the lower slide under the direction of weight was noted. The determinations were carried out in triplicate and the average of three reading is recorded.

c. Viscosity[11]: To evaluate rheological changes which occur when formulations with increasing amounts of water, a Brookfield viscometer were used to measure viscosity of amphiphilogel. The rotation was varied from 30 to 50 rpm at 25±1 ◦C. Measurements were made 3 times, using a fresh sample each time, i.e. n=3.

d. Determination of Extrudability

The extrudability of amphiphilogel formulations were determined by filling amphiphilogel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of amphiphilogel.

e. Measurement of pH [12]: The pH of the formulated amphiphilogel was determined using pH meter. The electrode was immersed in amphiphilogel and readings were recorded on pH meter.

f. Drug content [13]: For determination of drug content An amount equivalent to 50 mg of fluconazole was taken in a 50 ml volumetric flask then 30 ml of methanol was added. The flask was shaked for 10 min. finally the volume was made up to mark with methanol. The solution was filtered through Whatman filter paper. The sample was estimated analysed spectrophotometrically against blank at λmax 261 nm after proper dilution. The drug was estimated using standard calibration curve constructed in the same solvent.

g. *In vitro* drug release studies: The *in-vitro* drug release experiment was carried out by using fabricated Franz diffusion cell. The treated rat skin was cut into desired size and clamped between the receptor and donor compartments. The receptor compartment was filled with 13.2 ml of diffusion medium (Phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. The contents were stirred at about 50 r.p.m. by externally driven, teflon coated small magnetic bead to keep them well mixed. In order to attain 32.0 ^{o}C at the skin surface, receptor compartment was maintained at 37.5 oC. Accurately weighed 1 gm amphiphilogel was placed on the membrane. At suitable intervals, aliquots (3ml) were collected at preset time , then determined by measuring the absorbance at 261 nm using UV spectrophotometer (Shimadzu 160-A) after proper dilution. The diffusion medium of the same volume (3ml), which was pre warmed at 37 ^{o}C, was then replaced into the diffusion cell. Duration of the experiment was 1 to 8 hours.

h. Stability studies

The amphiphilogel were packed and kept for one month at 0^0c- 2^0c, 40^0c/ 75% RH in a stability chamber, 60^0c/80% in incubator [14]. At the interval of 15 days gel were withdrawn and evaluated for physical properties like Spreadibility, pH, viscosity and content uniformity carried out.

RESULTS AND DISCUSSION

Various organogels of Nonionic surfactants (Span 60, Tween 20/80) incorporating water were formulated

Physical characteristics of the Amphiphilogel

The formulated Amphiphilogel were tested for appearance, viscosity and feel. All Amphiphilogel were Transparent, translucent, and sudden viscosity changes. The post application feel of both Amphiphilogel were smooth and comfortable. The results are shown in Table.2

Table 2. Physical Characterization

Sr. No.	Parameters	Characterization
1.	Appearance	Translucent
2.	Colour	Transparent
3.	Sudden Viscosity change	No change
4.	Post Application feel	Smooth and comfortable

Physicochemical parameters of Amphiphilogel

The formulated Amphiphilogel were tested for Viscosity, spreadibility, Extrudability, pH, Drug content. The viscosity of various formulated fluconazole amphiphilo gels was measured using a Brookfield viscometer show in table.3. The rheological behaviour of all formulated gels system was studied and show in fig. 1.consistency depends on the ratio of solid fraction. The viscosity of all formulation was found from 16876- 21675. The spreadibility of amphiphilogel of fluconazole of all formulation was to be found from 48.61 ± 0.43 -62.05 ± 1.13

The drug content uniformity in the amphiphilogel of fluconazole of all formulation was to be found from 81.78 ± 0.78- 95.67 ± 0.34%. drug content uniformity in the amphiphilogel were show in table 3.

Batch Code	Spreadability (gcm/sec)±SD	Viscosity (centipoise)	Extrudability	pH	Drug content (%) ± SD
F1	55.72 ± 0.84	21654	277	5.82	85.67 ± 0.55
F2	59.82 ± 0.74	19554	266	5.65	88.75 ± 0.64
F3	48.61 ± 0.43	16876	329	5.45	95.67 ± 0.34
F4	62.05 ± 1.13	19654	276	5.75	92.17 ± 0.89
F5	48.17 ± 0.87	18798	297	5.45	81.78 ± 0.78
F6	54.43 ± 1.07	20878	287	5.48	92.76 ± 0.67
F7	57.66 ± 0.76	21876	267	5.86	89.67 ± 0.64
F8	60.19 ± 1.04	20486	318	5.54	86.57 ± 0.79

** Values are expressed in Mean ±SD, n=3*

In vitro Drug Release Study

Dissolution samples were analyzed by UV Spectroscopy method. The release of fluconazole was also dependant on the concentration of aqueous phase in the amphiphilo gel. The release rate was inversely proportional to the concentration of aqueous phase (water) i.e. higher the amount of water in the formulation lower the release rate. This is because, with increasing the amount of water present within the system, initially spherical reverse micelles transform into cylindrical micelles and then into long tubular and flexible micelles with ability to entangle and build up a three-dimensional network with a high viscosity. This network is responsible for the entrapment and unavailability of drug molecules for their release from the amphiphilogel system. It is also known that with an increase in the aqueous phase fraction, the droplet size increases. Hence, higher viscosity and enhanced droplet size due to greater amount of water could be responsible for decreased release of drug. The cumulative % drug release in the amphiphilogel of fluconazole of all formulation was to be found from 88.70- 96.48 %. The cumulative % drug release in the amphiphilogel were show in table 3 and Fig.2

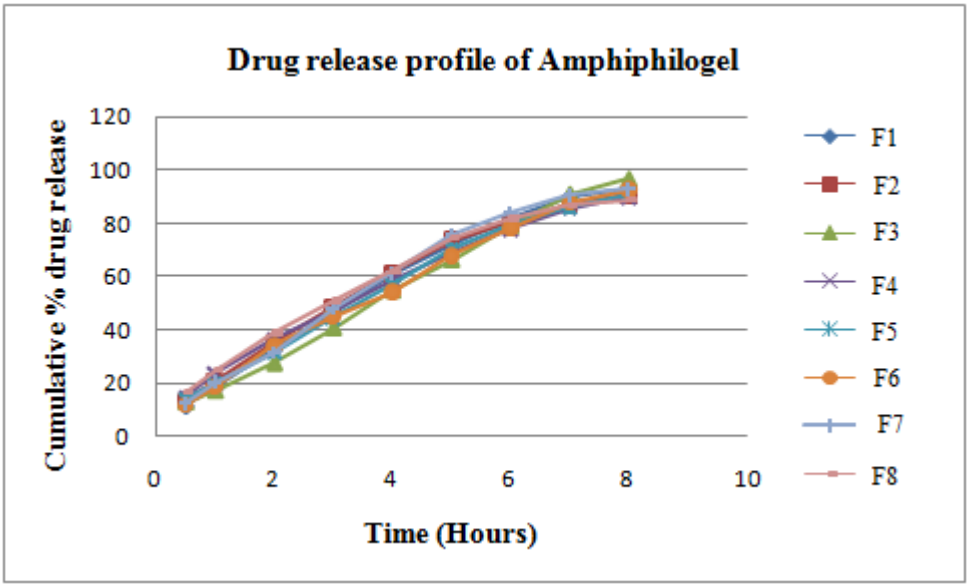

Fig.2 Percentage Drug release profile of Amphiphilogel.

Stability

The amphiphilogel formulation was found to be stable under the conditions of 0^{O} C and room temperature for the period of one monthat least.In 40^{o}C gel show low viscosity and low drug content hence it is not proper on above temperature. Stability study data were reported in table-4.

Table 4. Stability studies of amphiphilogel

S. No	Parameters	Storage Condition					
		0°C		25°C±2°C, 60% RH		40°C±2°C, 75% RH	
		15days	30days	15days	30days	15days	30days
1.	Spreadability (gcm/sec) ±SD	54.46±0.79	53.92± 0.78	55.65± 0.81	54.79± 0.47	53.55± 0.78	51.62 ± 0.74
2.	Viscosity (Centipoise)	15174	157678	16695	16687	13546	13959
3.	pH	5.47	5.49	5.48	5.48	5.53	5.58
4.	% Drug Contents	95.05± 0.44	95.10± 0.51	95.49± 0.45	95.55± 0.43	93.61± 0.65	93.08 ± 0.67

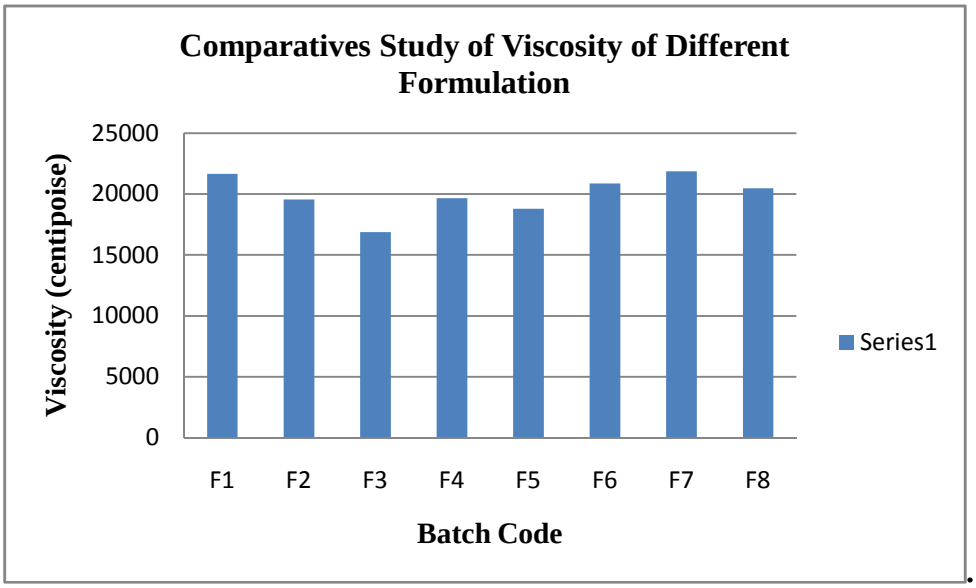

Fig. Comparatives Study of Viscosity of Different Formulation

CONCLUSION

From the above result and discussion it was found that the optimized amphiphilogel batch F3 was substantially stable at both room temperature and also at low temperature, thus storage at room temperature is possible. The cumulative % drug release in the amphiphilogel of fluconazole of all formulation was found within the range. From the above discussion it was concluded that the Successful formation and evaluation of amphiphilogel containing fluconazole to be done.

Acknowledgements
The authors are sincerely thankful to College of pharmacy, IPS Academy, Indore for providing us infrastructure facilities and moral support to carry out this research work. I sincerely express my gratitude to Glenmark generic ltd., Goa, India for providing fluconazole as a gift sample.

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