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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF MICONAZOLE TRANSFEROZOMAL GELS

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ABSTRACT
The present research work involves formulation and invitro evaluation of Miconazole transfersomal gel to reduce dosing frequency. The FTIR spectra revealed that there was no interaction between the drug and excipients. Transfersome formulations were prepared by hand shaking modified thin film hydration technique and were incorporated into 1.5% carbopol gel. The Formulation Mf7 containing Lecithin: Tween-80 has higher entrapment efficiency and maximum drug release. Stability studies performed for optimized transfersome gel formulations indicates that prepared transfersomes have more stability at lower temperature. Based on the above data, it was confirmed that prepared Miconazole, transfersomal gels can be considered as one of the promising approach to reduce the dosing frequency and to maintain drug concentration at the desired site for longer time.

Key Words: Miconazole, transfersomal gel

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INTRODUCTION
Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery is gaining importance recently because of certain advantages over the conventional oral route. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier of penetration across the skin which is stratum corneum cells are embedded in a pool of intercellular lipid lamellae. These lamellae have a crucial role in imparting barrier properties to the stratum corneum. As a result, only milligram quantities of drug can be delivered by this route. This limits the application of this route to only potent drugs. Extensive work has been done in order to overcome the barrier properties of intact human skin. These include augmentation of skin permeability using penetration enhancers, use of forces which are not dependent on concentration gradient (iontophoresis, electroporation, phonophoresis, microneedles, jet injectors, etc.,) and many more. Transfersomes or other drug carrier systems like vesicles belong to the latter category [1-4].Transfersomes are composed of phospholipids like

phosphatidyl choline which self assembles into lipid bilayer in aqueous environment and closes to form a vesicle. A bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) is added to increase lipid bilayer flexibility and permeability. This second component is called as edge activator. An edge activator consists usually of single chain surfactant that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity. The resulting, flexibility and permeability optimized, Transfersome vesicle can therefore adapt its shape to ambient easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. In its basic organization broadly similar to a liposome, the Transfersome thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane.The newer elastic vesicles were introduced by Van den berg in 1998, consisting of non ionic surfactant as the edge activator . Flexibility of transfersomes membrane canbe altered by mixing suitable surface active agents in the proper ratios. The resulting, flexibility and permeability optimized, Transfersome vesicle can therefore adapt its shape to surrounding stress easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. This flexibility also minimizes the risk of complete vesicle rupture in the skin and allows transfersomes to follow the natural water gradient across the epidermis, when applied under non occlusive condition [5]. Aim of the study is to prepare and evaluate Miconazole loaded transferosome gel.

MATERIALS AND METHODS

Preparation of Transfersomes by Modified Hand shaking lipid film hydration technique

Transfersomes were prepared by thin film hydration method using Miconazole, Soya Lecithin, and different concentrations of surfactants (Span-80, Tween80). The amount of drug is kept constant (50mg) in all the formulations. Different formulations (Table-1) were prepared by using different ratios of phospholipid and surfactants in different ratios. The details about the surfactants used and amount of lecithin and surfactant used in each formulation are given in the table no 5. Lecithin, surfactants and the drug are dissolved in 10ml of organic solvent (Chloroform: Methanol 1:1). The organic solvent is then removed by evaporation while hand shaking above lipid transition temperature (43^0c). Final traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the phosphate buffer (pH 6.8) by rotation at 60 rpm for 1 hour at room temperature. The resulting vesicles are swollen for 2 hours at room temperature. The multilamellar lipid vesicles (MLV) are then sonicated using sonicator for 30 minutes [6].

Table-1 Formulation of Miconazoletransferosomes

FORMULATION	Drug (mg)	Lecithin (mg)	Span 80 (mg)	Tween 80 (mg)
Mf1	50	90	10	--
Mf2	50	85	15	--
Mf3	50	80	20	--

Mf4	50	75	25	---
Mf5	50	90	--	10
Mf6	50	85	--	15
Mf7	50	80	--	20
Mf8	50	75	---	25

For all formulation choloroform and methanol(1:1 ratio) was added as solvent.

Preparation of transfersome gel

As a vehicle for incorporation of transfersomes for topical delivery, carbopol gels were prepared. Transfersomes aqueous dispersion was utilized for the formulation of topical gel. Polymer such as carbopol 934 was utilized to prepare transfersome gel. 1.50g of carbopol- 934 powder was dispersed into vigorously stirred (stirred by magnetic stirrerRemi 5MLH) in 100 ml distilled water (taking care to avoid the formation of in dispersible lumps) and allowed to hydrate for 24 hrs. The dispersion was neutralized with tri ethanolamine to adjust the pH [6.8] by using pH meter (Lab India Sab 5000) [7].

In-vitro **drug release studies**

In-vitro drug releasestudy was performed by usingModified Franz diffusion cell on egg membrane in phosphate buffer solution (pH 6.8) [8].Egg membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was $2cm^2$ and capacity of receptor compartment was 30ml of phosphate buffer (pH 6.8) maintained at 37 ± 0.5^0C and stirred by a magnetic bar at 100rpm. Transfersomal gel formulation equivalent to 5mg drug was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 5 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 6.8) to maintain sink conditions. The samples were analyzed spectrophotometrically at λ max 220nm.

RESULTS AND DISCUSSION

FTIR studies were performed to understand the compatibilities between the drug with different excipients. The figures above illustrate that the functional groups like **C-O** Stretching with the observation range of 1275-1200 has peaks at 1237.66 in pure drug and 1238.45 in optimized formulation. Similarly the functional group C –N Stretchinghas a peak range of 1250-1020 has peaks at 1022.10 in pure drug and 1021.12 in optimized formulation. The functional groups in both the pure drug and optimized formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study (Table-2).

Table-2 FTIR Interpretation table

Charecteristicpeak	**LITERATURE VALUES**	**OBSERVED VALUES**	
		Pure drug	**Optimized formulation**

C –O	1275-1200	1237.66	1238.45
C –N	1250-1020	1022.10	1021.12

The percentage entrapment of Miconazole was found to be maximum with formulation Mf7 because of the increase in the ratio of lipid volume in the vesicles as compared to the encapsulated aqueous volume. The effect of phospholipids and edge activator ratio in the lipid components of vesicles on the entrapment efficiency of lipophilic drug, the efficiency increased with increasing surfactant concentration and thus increased with increasing lipid concentration.

The results obtained shows 91.28 - 96.41 % drug content in all the formulations, which shows that there is no degradation of the drug in the process.The surface morphology was studied by Optical Microscopy The shapes of most of the Miconazole containing transfersomes were found to be spherical from SEM analysis (Fig-1).

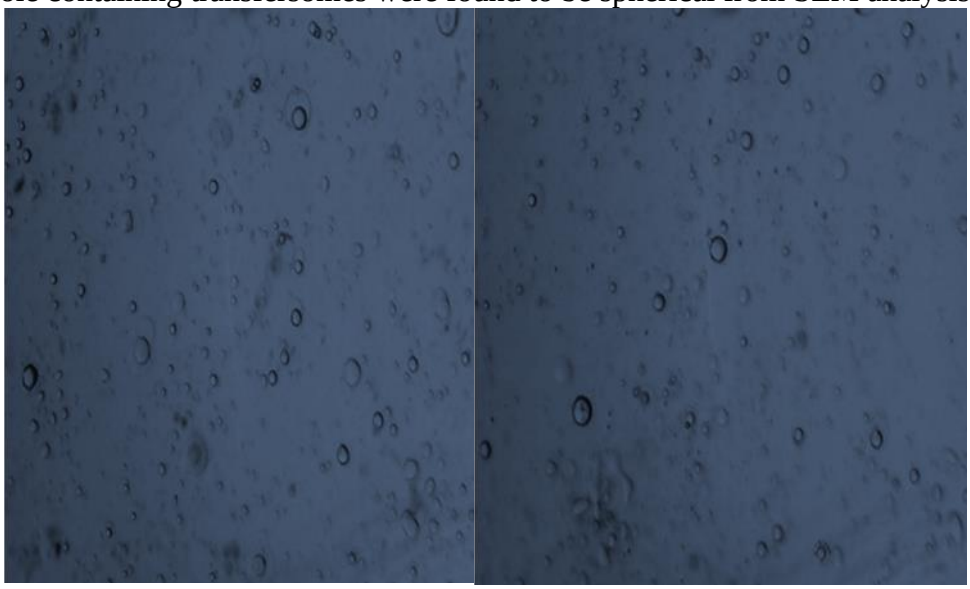

Fig-1 Photomicrograph of Miconazole loaded transfersome (Mf7) at 10X

The value of pH of topical transfersome gels was measured by using digital pH meter (LabindiaSab 5000 pH meter) at the room temperature. The pH of all topical transfersomal gels were found to be in the range of 6.1±0.34 to 6.7±0.54.The values are shown in Table-3.

Table-3 pH ,spreadability and viscosity of transferosomes

Formulation code	**pH**	**Viscosity**	**Spreadability (cm/sec)***
Mf1	6.1 ± 0.34	3310	3.4±0.11
Mf2	6.2±0.29	3570	2.7±0.16
Mf3	6.6±0.42	4150	3.2±0.22
Mf4	6.5±0.54	3650	3.6±0.14
Mf5	6.2±0.24	3700	3.5±0.46

Mf6	6.4±0.26	3600	3.4±0.21
Mf7	6.6±0.71	4550	3.7±0.19
Mf8	6.7±0.54	4000	3.4±0.22

The *in-vitro* diffusion study in phosphate buffer pH 6.8 were carried out using Franz diffusion cell according to procedure.The results are shown in Figure-2, 3.

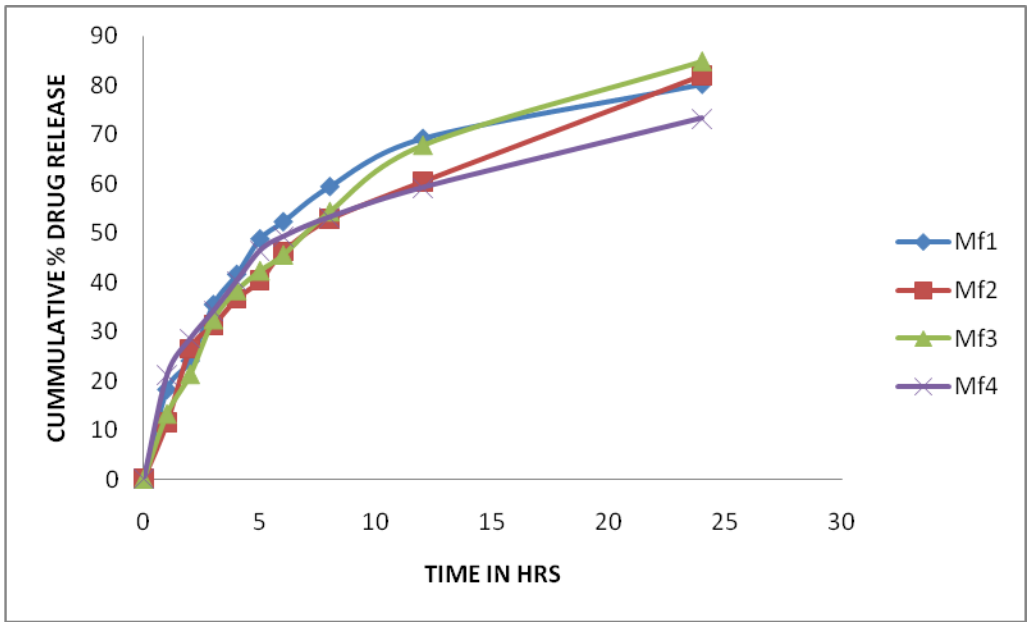

Fig-2 Comparative *IN-VITRO* drug release o formulations Mf1-Mf4

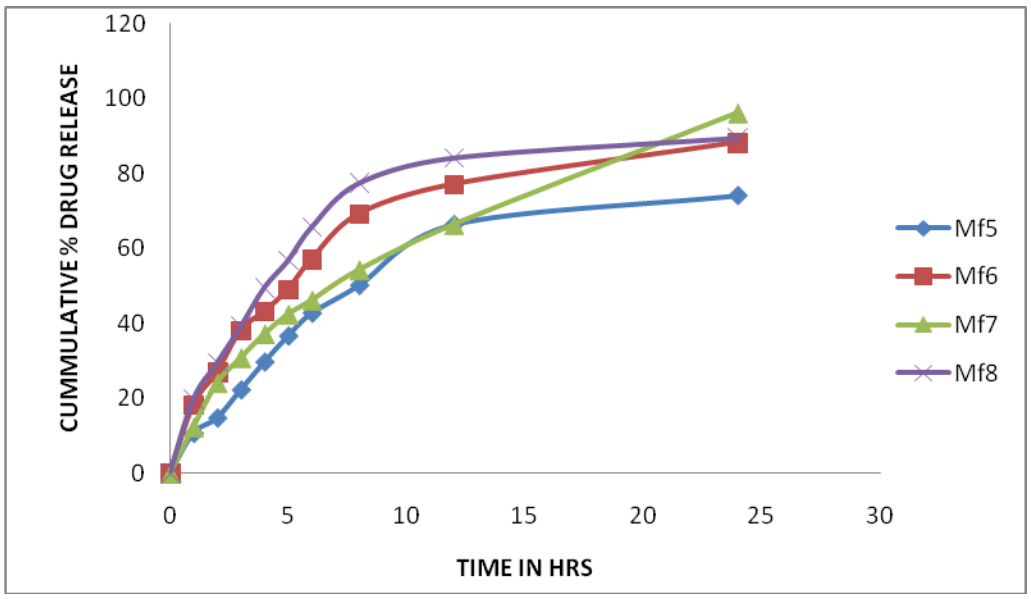

Fig-2 Comparative *IN-VITRO* drug release o formulations Mf5-Mf8

CONCLUSION

Over all the present work formulation of Miconazoletransfersomal gel has achieved all its objectives. The conclusions drawn from the project work are mentiond below.The results of this investigation indicate thathand shaking modified thin film hydration techniquecanbesuccessfullyemployedtofabricateMicon azoletransfersomal gel. FT-IR spectraof the physical mixture revealed thatthedrug is compatible with the polymers and copolymer used. Transferosomal gels containing carbopol and tween 80 and phospholipids has the highest entrapment efficiency compared to that of the other formulations.Increase in thepolymerconcentrationledto increase in,%Drugentrapment efficiency, Particle size. The *invitro* drug releasedecreased with increase in thepolymer and copolymerconcentration.Among all formulations Mf7 shows Maximum drug release when compared with other formulations.Analysis ofdrug release mechanism showedthatthedrug release fromthe formulations followed the Non fickian diffusion mechanism and follows First order kinectics.Based on the results of evaluation tests form ulation codedMf7 was concluded as best formulation.Finally, it can be concluded from the results of present study that transfersomal gel improve the transdermal delivery, and also overcome limitations associated with oral dosage forms. Miconazoletransfersomes creates a new opportunity for the well-controlled transdermal delivery of a number of drugs that have a problem of administration by other routes.

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