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FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF POSACONAZOLE TRANSFEROZOMAL GELS

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ABSTRACT

Posaconazole, a broad-spectrum triazole antifungal agent, is approved for the prevention of invasive as per gillosis and candidiasis in addition to the treatment of oropharyngeal candidiasis. There is evidence of efficacy in the treatment and prevention of rarer, more difficult-to-treat fungal infections. To alleviate this problem, vesicular drug delivery system transfersomes is formulated to deliver Posaconazole across skin and target drug to synovium or specific tissues which in turn increase drug efficacy with minimum extra synovial toxicity.The present research work involves formulation and in-vitro evaluation of Posaconazole transferosomal gel to reduce dosing frequency. The FTIR spectra revealed that there was no interaction between the drug and excipients. Transfersome formulations were prepared by thin film hydration technique and were incorporated into 1.5% carbapol gel. The Formulation PF7 containing Lecithin: Tween-80 in ratio 70:30 (%w/w) has higher entrapment efficiency and maximum drug release. *In-vitro* skin permeation study studies showed that,transfersome gels were found to increase the skin permeation and deposition showing a sustain effect. Stability studies performed for optimized transferosome gel formulations indicates that prepared transferosomes have more stability at lower temperature. Based on the above data, it was confirmed that prepared Posaconazole, transpersonal gels can be considered as one of the promising approaches to reduce the dosing frequency and to maintain drug concentration at the desired site for longer time.

Key Words: Posaconazole, transferosome gel formulations

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INTRODUCTION

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 associated primarily with outermost stratum corneum layer of epidermis. The skin structure looks as if

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.The flexible or deformable vesicles are called elastic vesicles or transfersomes. The concept and term of elastic vesicles was introduced first by by Gregor Cevc in 1991. Since then, huge amount of research is going on worldwide on these elastic vesicles under different titles like flexible vesicles, ethosome, etc. Transfersome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its proprietary drug delivery technology. The name means “carrying body”, and is derived from the Latin word 'transferre', meaning ‘to carry across’, and the Greek word ‘soma’, for a ‘body’. A Transfersome carrier is an artificial vesicle and resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery. In functional terms, it may be described as lipid droplet of such deformability that permits its easy penetration through the pores much smaller than the droplets size. It is a highly adaptable and stress-responsive, complex aggregate. When applied to the skin, the carrier searches and exploits hydrophilic pathways or 'pores' between the cells in the skin, which it opens wide enough to permit the entire vesicle to pass through together with its drug cargo, deforming itself extremely to accomplish this without losing its vesicular integrity. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimizing. This enables the Transfersome to cross various transport barriers efficiently. Transfersome penetrate the stratum corneum by either intracellular route or the transcellular route.Transfersomes were developed in order to take the advantage of phospholipids vesicles as transdermal drug carrier. These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency (1-4).The main objective of the study is to formulate and evaluate Posaconazole transferosome gel formulation for effective topical delivery of drug. Detailed literature survey revealed that commercial topical formulations of Posaconazole are available which have limited drug loading and requires frequent application. To overcome this problem Transferosome gel is prepared which helps in more penetration of drug and producing a sustain release effect at the site of administration.

MATERIALS AND METHODS

Preparation of Transferosomes by Modified Hand shaking lipid film hydration technique

Transferosomes were prepared by thin film hydration method using posaconazole, Soya Lecithin, and different concentrations of surfactants (Span-20, Tween80). The amount of drug is kept constant (100mg) in all the formulations. Different formulations 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-1. 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 (5, 6).

Table-1 Formulation of Posaconazole transferosomes

Formulation	Posaconazole (mg)	Soya Lecithin (mg)	Span 20 (mg)	Tween 80 (mg)	Chloroform (ml)	Methanol (ml)
PF1	100	90	10	--	5	5
PF2	100	80	20	--	5	5
PF3	100	70	30	--	5	5
PF4	100	60	40	---	5	5
PF5	100	90	--	10	5	5
PF6	100	80	--	20	5	5
PF7	100	70	--	30	5	5
PF8	100	60	---	40	5	5

Preparation of Posaconazole 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 stirrer Remi 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 (7, 8).

Scanning electron microscopy (SEM)

The morphology of the posaconazole transferosomal gel was studied using scanning electron microscopy (SEM).The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold film under reduced pressure. The stub containing the coated samples was placed in the scanning electron microscope (Hitachi S3400N) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 5 kV. Microphotographs were taken on different magnification and higher magnification was used for surface morphology.

***In-vitro* diffusion drug release studies**

In-vitro drug release studies from posaconazole transferosomal gel were performed by using Modified Franz diffusion cell on egg membrane in phosphate buffer solution (pH 6.8). 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 (9).

RESULTS AND DISCUSSION

FTIR studies were performed to understand the compatibilities between the drug with different excipients. The functional groups like O-H Stretching with the observation range of 3300-2500 has peaks at 2950.13 in pure drug, 2951.71 drug and execipient(soya lecithin)and 2985.14 drug and execipient(carbopol). Similarly the functional

group C –O Stretchinghas a peak range of 1210-1160 has peaks at 1160.97 in pure drug 1161.46 drug and execipient(soya lecithin)and 1161.63 drug and execipient(carbopol).Similarly the functional group C ═O strongStretching has a peak range of 1870-1540 has peaks at 1587.01 in pure drug 1587.01 drug and execipient(soya lecithin)and 1587.38 drug and execipient(carbopol).C-F strongStretching has a peak range of 1400-1000 has peaks at 1383.76 in pure drug 1384.30 drug and execipient(soya lecithin)and 1383.53 drug and execipient(carbopol).The functional groups in both the pure drug and Execipient formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study. The % entrapment efficiency of deformable vesicles formulations were found to be in the range of 80.41 to 86.26 were shown in Fig-1.Entrapment efficiency of the PF7 formulation was high (maximum 86.26).% drug content of transferosome formulations were determined according to procedure described. The results obtained shows 91.47- 96.45% drug content in the formulations. The results obtained are shown in Fig-2.

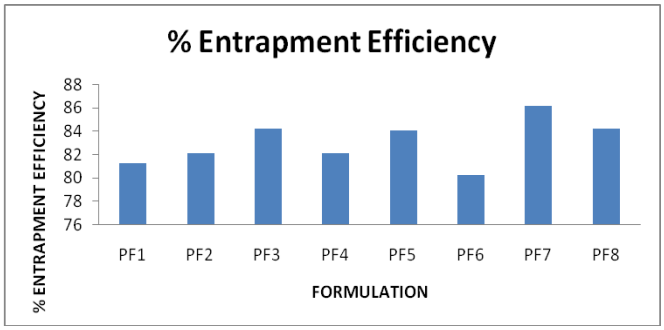

Fig-1 % Entrapment efficiency for PF1 –PF 8

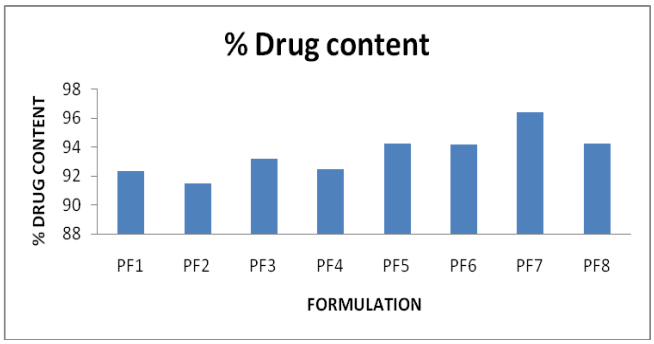

Fig-2 %Drug content for PF1 –PF8

The percentage entrapment of Posaconazole was found to be maximum with formulation PF7 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 edgeactivator 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 91.48 -96.41 % drug content in all the formulations, which shows that there is no degradation of the drug in the process.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 Fig-3 and 4.

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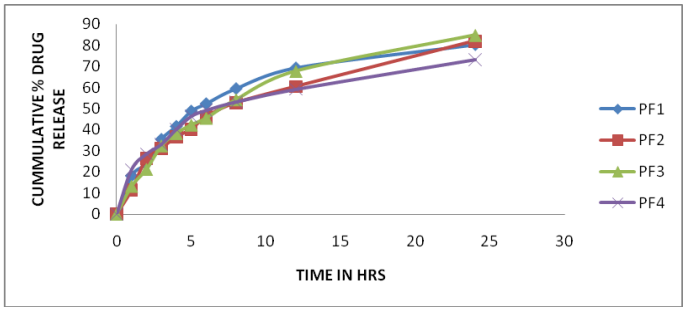

Fig-3 Comparative *IN-VITRO* drug release of formulations PF1-PF4

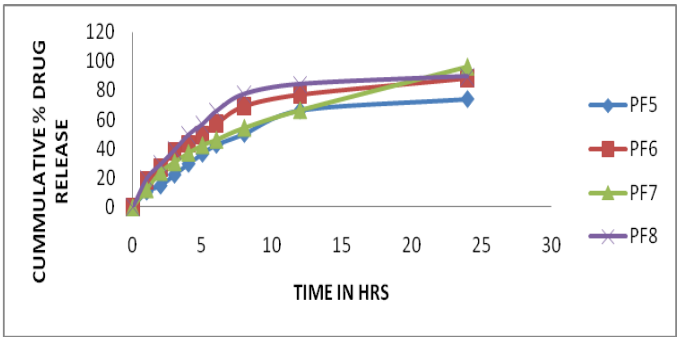

Fig-4 Comparative *In-Vitro*drug release of formulations PF5-PF8

The in-vitro drug release from the formulations was studied using franz diffusion cell for a period of 24 hours. The cumulative % drug release was calculated. Among the formulation PF1 having lecithin(90mg) and span 20 (10mg) and chloroform &methaol in the ratio 1:1(10ml) registered drug release of 80.24%. The drug release consequently increased on increasing the amount of span20 in the formulations PF2 and PF3. The formulation PF2 had drug release of 84.% in 24 hours and formulation PF3 with 84.8% after 24 hours. The presence of lecithin decreases invitro residence time. The formulation PF4 belonging to gelatin series with lecithin showed drug release of 74.28%after 24 hours. The poor drug release might be due to the influence of lecithin. The amount of hydrophilic polymer gelatin is increased in formulations PF5 and PF6. The gelatin swells in presence of water thereby increases the drug release but at the same time it influences the bio adhesion of the formulation with mucosa. The formulation PF5 with lecithin(90mg) and tween 80(10mg) showed drug release of 76.14% in 24 hours. The formulation PF6 having lecithin(80mg) and tween 80 (20mg) had the drug release of 88.35% in 24 hours. The formulation PF7 having lecithin(70mg) and tween 80 (30mg) had the drug highest release of 96.18% in 24 hours. The formulation PF8 having lecithin(60mg) and tween 80 (40mg) had the drug release of 89.46% in 24 hours. Formulation PF7 had the highest drug release upto 24hrs. Comparison of results obtained from diffusion studies for all eight formulations have been done. It was found that formulation PF7 shows higher drug release rate than other formulations. This result of diffusion profile showed slight initial burst release. This is probably caused by the release of drug absorbed on the transferosome surface or precipitated from the superficial lipid layer. Prolonged release in the later stage can be attributed to the slow diffusion of the drug from the lipid vesicle.The transferosomes were subjected to microscopic examination (S.E.M) for characterizing size and shape of the transferosomes. Microscopic examination revealed, spherical small unilamellar esicles size (Fig-5).

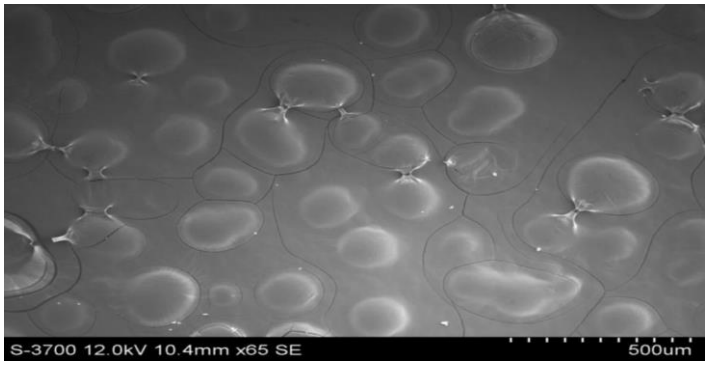

Fig-5 SEM analysis of optimized formulation (PF7)

The dissolution data was subjected to regression analysis and were fitted to kinetic models, viz., Zero order. It was found that PF7 Optimised formulation followed first order (R^2=0.966). It describes the systems where the drug release rate is independent on its concentration. The drug release mechanism is identified as following higuchi model(diffusion).

CONCLUSION

Posaconazole, a broad-spectrum triazole antifungal agent, is approved for the prevention of invasive aspergillosis and candidiasis in addition to the treatment of oropharyngeal candidiasis. There is evidence of efficacy in the treatment and prevention of rarer, moredifficult-to-treat fungal infections. To alleviate this problem, vesicular drug delivery system transfersomes is formulated to deliver Posaconazole across skin and target drug to synovium or specific tissues which in turn increase drug efficacy with minimum extra synovial toxicity.Finally, it can be concluded from the results of present study that transfersome gel improve the transdermal delivery, prolong the release, and improve the site specificity of the drug Posaconazole. Transfersomes formed from Lecithin: Tween80 in the ratio 70:30 (%w/w) is a promising approach to improve the permeability of posaconazole in period of time. Transfersomes 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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