Formulation and in-vitro Evaluation of Terbinafine HCl Loaded Ungual Liposomal Gels

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ABSTRACT SUMMARY

Liposomes are phospholipidic vesicular systems and ethosomes are versus of classic liposomes which contain high amount of ethanol. Gel systems were chosen as vehicle for topical application of liposomal preparations. Poloxamer 407, chitosan and carbopol were used as gelling agents.

This study reported the development and in-vitro release and rheologic evaluation of liposome and ethosome gel formulations for ungual drug delivery. The dialysis bag diffusion technique was used to study the in-vitro drug release of TBF-HCl.

The release study showed that poloxamer had no effect on release profile of liposome. Therefore poloxamer is a suitable polymer for ungual application of liposome. On the other hand, gel system could not be formed for ethosome formulation with poloxamer. Drug release was found higher for liposome and ethosome suspension than liposome and ethosome in chitosan and carbopol gel formulations.

INTRODUCTION

A topical antifungal product must overcome the nail barrier for successful treatment of onychomycosis (1). Liposomes are colloidal phospholipidic vesicles extensively investigated as safe and effective drug carrier systems. Among their several possible pharmaceutical applications, they have been widely applied in topical drug delivery (2). Ethosomes contain phospholipids, alcohol in relatively high concentration and water (3). Liposome and ethosome vesicles embedded into a suitable gel matrix, could be attractive candidates for topical application of antifungal agents.

Chitosan, poloxamer and carbopol were chosen as gel agents due to advantageous biological properties.

The aim of our study was to formulate and evaluate in vitro release and reological behaviour of TBF-HCl liposome and ethosome gels for ungual application.

EXPERIMENTAL METHODS

Preparation of Liposome and Ethosome Formulations

The thin film hydration method was used to prepare the liposomal suspension. Phospholipid, cholesterol and TBF-HCl were dissolved in chloroform, and organic solvent was evaporated to form a thin film. Subsequently, the resulting thin film was hydrated in pH 7.4 phosphate buffer (2).

Ethosomal formulations were prepared according to the method reported by Touitou (3). Phospholipids and TBF-HCl were dissolved in ethanol. The aqueous phase was added slowly to the lipid mixture with constant stirring at 700 rpm. The liposomal and ethosomal suspensions were homogenized by sonication (Bandelin UW 2070).

Preparation of Liposome and Ethosome Gel Formulations

The liposome poloxamer gel (J1) was prepared by adding the required amount of poloxamer 407 (20% w:w) in small quantities to the cold TBF-HCl containing liposomal solution (4°C), and letting it slowly dissolve under gentle stirring with a magnetic bar.

The weighed amount of chitosan (3% w:w) was mixed with liposome (J2) and ethosome (J4) suspensions. Glacial acetic acid was added and stirred slowly. Gel was kept at room temperature overnight before the application.

Carbopol (2% w:w) was added liposomal (J3) and ethosomal (J5) suspensions and suspension gently stirred for the gel swell. Triethanolamine was added with continuous stirring to form a transparent gel until the gel was alkaline.

In-vitro Drug Release

The dialysis bag diffusion technique was used to study the in-vitro drug release of TBF-HCl. 1g of liposome and ethosome gel formulation were placed in the dialysis bag, hermetically sealed and immersed into 150 ml of ethanol:water mixture. Samples were withdrawn from the receptor compartment at predetermined time intervals and the amount of drug released was determined by HPLC.

The HPLC system is consisting of a UV/Vis detector and a reverse phase Nucleodur®C18 column. A filtered and degassed solution containing 75% (V/V) acetonitrile, 20% (V/V) KH2PO4 buffer (pH 4.5) and 5% (V/V) tetrahydrofuran was used as the mobile phase at flow rate of 0.9 ml/min. The peak area correlated linearly with Terbinafine HCl concentrations in the range of 0.05-30 µg/ml (r²= 0.999). The validation of the method was accomplished on the specificity, stability, the accuracy, and the precision (4).

Rheological studies

The rheological analysis of the formulations was performed both at 20 ± 0.1°C (data was not shown) and 32 ± 0.1°C using an AR 2000 controlled stress/controlled rate rheometer, in flow mode, and in conjunction with parallel steel plate geometry (40 mm diameter). In continuous shear analysis, upward and downward flow curves for each formulation were measured over shear rates ranging from 10–900 s⁻¹.
RESULTS AND DISCUSSION

Figure 1-2 illustrates the released amount of TBF-HCl from formulations. In Figure 1 the liposome formulation showed slower release than ethosome due to permeation enhancer effect of ethanol in ethosome formulation.

The release amounts of TBF-HCl from liposome chitosan and carbopol gels were found nearly the same (Figure 2). By the way the release of TBF-HCl from chitosan gel was slower than carbopol gel. The release amount of TBF-HCl was decreased in comparison with the liposome suspension. The poloxamer had no affect release of TBF-HCl in comparison with the liposome suspension.

As shown in Figure 2, a slight difference was observed with ethosome carbopol and chitosan gel formulations at the end of 24h. By the way, the release from carbopol gel was faster than chitosan. And also ethosome gels have higher release rate in comparison with liposome gels (J2-J3). But the release decreased as the formulation formed a gel system for ethosome.

Representative flow curves were graphically presented in Figure 3. The shear stress changes upon shear rates have been used to determine whether the rheological behavior of the formulation is Newtonian or non-Newtonian. In continuous shear rheometry, formulations exhibited pseudo-plastic flow at 32°C. A rapid increase in shear stress was observed most clearly with poloxamer formulation.

CONCLUSION

A gel system could not be obtained with poloxamer for ethosomal formulation. It was concluded that ethanol affected gelation of system (5).

As a conclusion, liposomal and ethosomal gel formulations could be prepared successfully while the aim is prolonged release. But, liposomal poloxamer gel formulation could be suggested as promising systems for topical drug delivery due to fast release profile and easier application of vesicular suspension. Further studies are in progress.

REFERENCES