Formulation and Evaluation of Miconazole Niosomes

P.U. Mohamed Firthouse*, S. Mohamed Halith, S. U. Wahab, M. Sirajudeen, S. Kadher Mohideen

Fathima College of Pharmacy, Kadayanallur 627751, Tamilnadu, India.

*Corres. author: mohamedpu@rediffmail.com

Abstract: This study was to investigate the feasibility of using niosome as a transdermal drug delivery system for Miconazole. Topically applied niosomes can increase residence time of drug in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. It also improves the horny layer properties both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids. Miconazole is a imidazole antifungal agent used in the treatment of candida infections, fungal infections. Niosome was prepared by Thin Film Hydration Technique. Miconazole niosomes were prepared by varying the cholesterol and surfactant ratios as 1:0.5, 1:1, 1:1.5. Each formulation was evaluated for percentage of drug entrapment and for their cumulative drug release. formulation with 1:1 CHOL: SA ratio, the concentration of SA was increased and it has shown 92.10 % drug release in 24 hours. The release showing required amount of drug release per day as well as extended for the required day is the optimized formulation. Hence, B formulation is the optimized one.

Key words: Niosomes, Gel, invitro studies, miconazole.

Introduction

Niosomes are non ionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. Niosomes are either unilamellar or multilamellar vesicles that have a better stability than liposomes. Niosomes are formed on admixture of nonionic surfactant, cholesterol with subsequent hydration in aqueous medium. In addition of cholesterol, which gives the rigidity to the bilayer and results in less leaky niosomes. Niosome behave invivo like liposomes prolonging the circulation of entrapped drug and altering its organ distribution.

This study was to investigate the feasibility of using niosome as a transdermal drug delivery system for Miconazole. Niosomes offer a versatile vesicle delivery concept with potential for delivering drug via transdermal route. Topically applied niosomes can increase residence time of drug in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. It also improves the horny layer properties both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids. Miconazole is a imidazole antifungal agent used in the treatment of candida infections, fungal infections. Miconazole is available as conventional dosage forms like powders, parenterals, gels, creams and ointments in the market. The conventional dosage form of this drug has several side effects like nausea, vomiting and abnormalities of liver enzymes.

Better targeting of drugs to the infected organs can be achieved by niosomal formulation due to the presence non-ionic surfactants with lipids. The presence of nonionic surfactants increase the permeability of Miconazole through the biological membrane and also reduces the systemic toxicity of anti-infective drugs. Thus the therapeutic index of the Miconazole can be improved when given in niosomal formulation.
Materials and Methods

Miconazole gift sample from Micro Labs, Hosur. Cholesterol, Span received from S.D.Fine Chem Ltd. Triton X 100 from Loba Chemie. Remaining all the ingredients used were AR grade.

Formulation of Miconazole Niosome

Niosome was prepared by Thin Film Hydration Technique. Accurately weighed quantity of cholesterol and surfactant were dissolved in chloroform – methanol mixture (1:1 v/v) in 100 ml round bottom flask. The weighed quantity of drug is added to the solvent mixture. The solvent mixture was removed from liquid phase by flash evaporation at 60°C to obtain a thin film on the wall of the flask at a rotation speed of 150 rpm. The complete removal of residual solvent can be ensured by applying vaccum. The dry lipid film was hydrated with 5 ml phosphate buffer saline of pH 7.4 at a temperature of 60 ± 2°C for a period of 1 hour until the formation of niosomes. The ratios of the formulations were 1:0.5, 1:1, 1:1.5 of cholesterol : surfactant. The batch codes were A1 to A3.

Removal of unentrapped drug from Niosome

The unentrapped drug from niosome was removed by dialysis method. Niosome suspension was placed in 3cm x 8cm long dialysis bag whose molecular weight cut off was 12,000. The dialysis bag was then placed in 250 ml beaker containing phosphate buffer saline of pH 7.4 at a temperature of 60 ± 2°C for a period of 1 hour until the formation of niosomes. The ratios of the formulations were 1:0.5, 1:1, 1:1.5 of cholesterol : surfactant. The batch codes were A1 to A3.

Size Analysis

By optical microscopy

A drop of niosome suspension was placed on a glass slide and it was diluted. A cover slip was placed over the diluted niosome suspension and evaluated the average vesicle size and shape by an ordinary optical microscope using a precalibrated ocular eye piece micrometer.

Percentage Encapsulation of drug

Vesicles containing Miconazole were separated from unencapsulated drug by dialysis. Niosomal preparation of 0.5 ml was taken after dialysis. To this 0.5 ml of 10% triton X – 100 was added and incubated for 1 hour. The triton X–100 was added to lyse the vesicles in order to release the encapsulated Miconazole. Then it was diluted with phosphate buffer saline solution (pH 7.4) and filtered through whatmann filter paper. The filtrate was measured spectrophotometrically at 424 nm using phosphate buffer and triton X – 100 mixture as blank. From the absorbance value, the concentration of drug in mcg/ml was found using the standard curve

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\text{Percentage drug loading (PDL)} = \frac{\text{Entrapped drug (mg)}}{\text{Total Drug Added (mg)}}
\]

In vitro release study for niosomal formulations and analysis by UV method

Niosomal preparation was taken in a dialysis membrane of 5 cm length and suitably suspended in a beaker containing 200 ml of diffusion medium (Phosphate buffer saline pH 7.4). The medium was maintained at a temperature of 37 ± 0.5°C. It was stirred by means of magnetic stirrer at a constant speed. Sample of 2 ml (diffusion medium) was withdrawn at every 24 hours for 8 days and replaced the diffusion medium, so that the volume of diffusion medium was maintained constant at 200 ml. The samples were measured spectrophotometrically at 424 nm. The release was compared with a marketed Miconazole gel.

Formulation of Niosomal Gel

The gel formulation was prepared by incorporating the optimized formulation into a suitable gel base. The gel base selected for incorporation of niosomes with SCMC base.

Gel Formulated with SCMC base

Miconazole niosomal suspension
Sodium carboxy methyl cellulose (SCMC)
Glycerine
Distilled water

SCMC used as gallant soaked in water, glycerin used as humectants, required quantity of gel prepared, and make up with water the add niosomal suspension.

Table : 1 Composition of Miconazole niosomes

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miconazole (mg)</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>200µgm</td>
<td>200µgm</td>
<td>200µgm</td>
</tr>
<tr>
<td>Span40 (mg)</td>
<td>100µgm</td>
<td>200µgm</td>
<td>300µgm</td>
</tr>
</tbody>
</table>
Table 2. Vesicle size and Entrapment efficiency of Miconazole Niosomes

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Cholesterol Surfactant Ratio</th>
<th>Surfactant Used</th>
<th>Percentage Entrapped drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>1:0.5</td>
<td></td>
<td>80.5 ± 0.51</td>
</tr>
<tr>
<td>A2</td>
<td>1:1</td>
<td>Span 60</td>
<td>97.01 ± 0.14</td>
</tr>
<tr>
<td>A3</td>
<td>1:1.5</td>
<td></td>
<td>89 ± 0.43</td>
</tr>
</tbody>
</table>

Results and Discussion

Formulation of Miconazole Niosomes

Based on the above optimized parameters, Miconazole niosomes were prepared by varying the cholesterol and surfactant ratios as 1:0.5, 1:1, 1:1.5. Each formulation was evaluated for percentage of drug entrapment and for their cumulative drug release.

Removal of unentrapped drug from Niosome

As the amount of surfactant increased, the amount of dialysed Miconazole was also increasing 1:1 ratio indicates that concentration of surfactant used should be optimum so that more amount of drug can be in the encapsulated form for an extended release.

Among all the formulations, the dialysed quantity of batch A3 (Cholesterol : Span 60 : : 1 : 1) was maximum .The result indicated more amount of Miconazole in an encapsulated form.

Size Analysis

Size analyzed performed by optical microscopy. niosomes have spherical in nature.

Entrapment Efficiency:

After the removal of unentrapped drug by dialysis, the entrapment efficiency of all the formulations was studied. The various factors like lipid concentration, drug to lipid ratio, cholesterol
content will change the entrapment efficiency. The lipophilicity also influences the entrapment of drug. The formulation B2 with Cholesterol and Span 60 in the ratio of 1:1.5 showed entrapment efficiency of 97%.

The formulation D4, Cholesterol : Tween 20 = 1 : 2.5 showed low entrapment efficiency among all formulations. It showed a entrapment of 68.5%.

The formulation A1 showed a percentage entrapment of 97% which was formulated with a ratio of 1:1 (Cholesterol : Span40) Hence the Miconazole niosome formulated with Span 40 and Span 60 with ratio 1:1 and 1:1.5 respectively were found to be optimum for loading maximum amount of Miconazole in niosomal formulation.

**In vitro release study for niosomal formulations and analysis by UV method**

*In vitro* release was found to be biphasic as the release was controlled by the dialysis membrane and the lipid bilayer. Incorporation of cholesterol affected the release rate of the encapsulated drug.

A formulation with 1:0.5 CHOL: SA ratio has shown only 71.80 % drug release in a 20 hours period. In B formulation with 1:1 CHOL: SA ratio, the concentration of SA was increased and it has shown 92.10 % drug release in 24 hours. In C formulation with 1:1.5 CHOL: SA ratio has shown 82.18 % drug release in 22 hours.

The amount of cholesterol in the lipid phase (1:1.5 CHOL: SA ) shows its significance in the release rate of miconazole, release of it is decreased, which could be related to increased rigidity of the phospholipids bilayer, followed by its decreased permeability for the encapsulated drug. The release showing required amount of drug release per day as well as extended for the required day is the optimized formulation. Hence, B formulation is the optimized one.

**Kinetics of drug release**

The optimized formulation A2 was subjected to graphical treatment to assess the kinetics of drug release. A plot of concentration versus time showed linearity in optimized formulation of Miconazole Niosome. Hence it follows zero order kinetics. Higuchi’s plot confirms that the release is diffusion mediated.

**Conclusion**

An effort was made to formulate the Miconazole Niosomes and incorporate the Niosomes into the gel. From the results of the present experiments it may be concluded that formulation A2 containing 1:1. was showing high percentage of entrapment and desired sustained release of Miconazole. Hence B2 formulation was the optimized one. The optimized formulation B2 was found to follow zero order release pattern which was revealed by the linearity shown from the plot of time versus concentration.

**References**


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