



FORMULATION AND EVALUATION OF METOPROLOL TARTRATE ENTRAPPED NIOSOMES

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ABSTRACT

Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic and hydrophilic drugs. Niosomes have been prepared with different surfactants. Different batches of metoprolol tartrate niosomes were prepared by changing the surfactant concentration but keeping the cholesterol concentration constant. The prepared niosomes were characterized for particle size, entrapment efficiency and drug release studies. It was observed that Span 60 based formulations have higher entrapment efficiency than other formulations. Also Span 80 based formulations produced vesicles of smallest size and maximum cumulative percent drug release. In conclusion, the niosomal formulation could be a promising delivery system for metoprolol tartrate.

Key words: Niosomes, Metoprolol tartrate, Tween 60, Tween 80, Span 60, Span 80

INTRODUCTION

Drug delivery system using colloidal particulate carrier such as liposomes and niosomes has distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs¹. Niosomes are formation of vesicles by hydrating mixture of cholesterol and nonionic surfactants. These nonionic surfactants are called niosomes². They are osmotically active and are stable of their own, while also increasing the stability of entrapped drugs³. Handling and storage of surfactants require no special conditions. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result; can accommodate drug molecules with a wide range of solubilities. They exhibit flexibility in structural characteristics (composition, fluidity, size) and can be designed according to the desired situation⁴. Due to their capability to carry a wide variety of

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drugs, these lipid vesicles have been extensively used in various drug delivery systems⁵ like drug targeting⁶, controlled release⁷ and permeation enhancement of drugs⁸.

The transdermal route of drug delivery has many advantages for administration of drugs in local and systemic therapy. But skin is widely recognized for its effective barrier properties compared with other biological membranes. The low permeability of the skin makes it a minor port of entry for drug. The vesicular drug delivery is thus potentially beneficial as vesicles tend to fuse and adhere to the cell surface; this is believed to increase the thermodynamic activity gradient of the drug at vesicle stratum corneum interface and thus, leading to enhanced permeation⁹.

Metoprolol tartrate, a beta 1 selective adrenergic blocking agent, has become well established as a first choice of drug in the treatment of mild to moderate hypertension and stable angina and is beneficial in post infarction patients¹⁰. It is almost completely absorbed after oral administration, but bioavailability is relatively low because of hepatic first pass metabolism. The half life is about 3 to 4 hours¹¹. In the present work, an attempt has been made to prepare and evaluate niosomes of metoprolol tartrate that can continuously deliver therapeutically significant levels of drug for prolong time period.

EXPERIMENTAL

Materials

Metoprolol tartrate was obtained as a gift sample from Torrent Pharmaceuticals, Gandhinagar. Span 80, Span 60 (CDH (P) Ltd., New Delhi), Tween 80, Tween 60 (S. D. Fine Chem. Ltd., Mumbai) and Cholesterol (Loba chemie Pvt. Ltd., Mumbai) were used. Dialysis membrane was purchased from Himedia Laboratories Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade.

Methods

Formulation of metoprolol tartrate entrapped niosomes

Niosomes were prepared by the conventional thin film hydration method¹². Four different surfactants viz. Span 80, Span 60, Tween 80 and Tween 60 were used for the preparation of niosomes. Four different drug surfactant ratios viz. 1 : 0.5, 1 : 1, 1 : 1.5 and 1 : 2 were taken. The concentration of cholesterol was kept constant in all formulations. The drug and cholesterol ratio was similar in all formulations. Drug, nonionic surfactant and cholesterol were weighed and dissolved in chloroform in a round bottom flask. The solvent was evaporated at a temperature of 60°C under reduced pressure on a rotary evaporator to

form a thin film on the flask wall. The resulting film was hydrated with phosphate buffer pH 7.4 for 30 minutes at room temperature with gentle shaking. This results in the formation of niosomes, which was confirmed after microscopic examination of the suspension using 45X magnification. The composition, ratio and code of the niosome formulations are given in Table 1.

Table 1: Compositions, entrapment efficiency and particle size of niosomes

Formulation code	Ratio (Drug : Surf : Cholesterol)	Particle size (μm)	Entrapment efficiency (%)
FS80 ₁	1 : 0.5 : 1	5.35	82.46
FS80 ₂	1 : 1 : 1	5.23	84.64
FS80 ₃	1 : 1.5 : 1	5.20	84.26
FS80 ₄	1 : 2 : 1	5.00	86.82
FS60 ₁	1 : 0.5 : 1	5.77	88.68
FS60 ₂	1 : 1 : 1	5.63	88.74
FS60 ₃	1 : 1.5 : 1	5.47	88.62
FS60 ₄	1 : 2 : 1	5.42	89.82
FT80 ₁	1 : 0.5 : 1	6.92	68.05
FT80 ₂	1 : 1 : 1	6.88	69.45
FT80 ₃	1 : 1.5 : 1	6.77	64.84
FT80 ₄	1 : 2 : 1	6.57	65.72
FT60 ₁	1 : 0.5 : 1	6.44	68.34
FT60 ₂	1 : 1 : 1	6.32	66.55
FT60 ₃	1 : 1.5 : 1	6.26	64.18
FT60 ₄	1 : 2 : 1	6.00	63.43

Characterization of niosomes

(i) Particle size

The hydrated niosome dispersion was observed using optical microscopy. After suitable dilution, the niosomes was placed on glass slide and viewed by a microscope with a magnification of 45X¹³.

(ii) Entrapment efficiency

Niosomes containing metoprolol tartrate were separated from untrapped drug by centrifugation method. The drug remaining entrapped in niosome is determined by complete vesicle disruption using 50 % n-propanol and was calculated as¹⁴ -

$$\text{Entrapment efficiency} = A_e \times 100/A_i \quad \dots(1)$$

Where, A_e is the amount of entrapped drug and A_i is the total amount of drug added.

(iii) *In vitro* drug release

Drug release studies were carried out using hollow glass cylinder made up of borosil glass. One end of the cylinder was covered with Himedia dialysis membrane, which was previously soaked in warm water. The receptor cell was filled with pH 7.4 phosphate buffer. The receptor cell contained a magnetic bead and was rotated at a constant speed. Samples were withdrawn and replaced with fresh buffer at regular intervals of 1 hour for 12 hours until whole of encapsulated drug was released from the formulation. The samples were analyzed spectrophotometrically after suitable dilutions at 223 nm and the percentage of drug release was calculated by taking the estimated amount of the drug encapsulated as 100 %¹⁵. The results are tabulated in Table 1.

RESULTS AND DISCUSSION

Metoprolol tartrate entrapped niosomes were prepared by thin film hydration technique. Span 80, Span 60, Tween 80 and Tween 60 were selected as non-ionic surfactants for preparation of niosomes. Four different ratios (0.5 : 1 : 1, 1 : 1 : 1, 1.5 : 1 : 1, 2 : 1 : 1) of surfactant, cholesterol and drug were taken for preparing metoprolol tartrate entrapped niosomes. *In vitro* evaluation of prepared niosomes was carried out by measuring the particle size, entrapment efficiency and percent drug release patterns.

Determination of vesicle size is important for the topical application. Vesicle size was found to be smallest for FS80₄ formulation. The particle size range was found to be 5.00 to 6.92 μm for all formulations. Increasing hydrophobicity of the surfactant monomer led to a smaller vesicle; a result that is expected since surface free energy decreases with increasing hydrophobicity. Therefore, the size of the vesicles is dependent on the hydrophile-lipophile balance of the surfactant used; the lower is the HLB, the smaller will be the initial size of the vesicles.

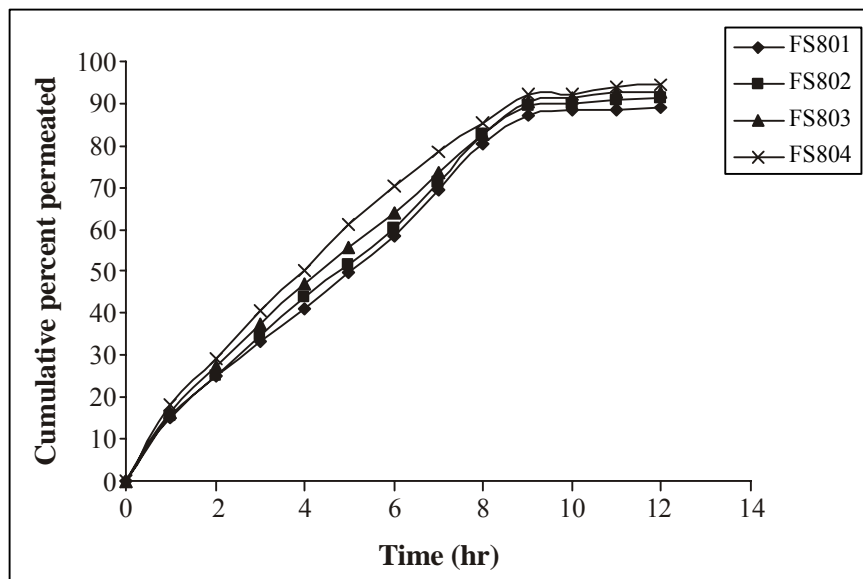


Fig. 1: Release profile of Span 80 niosome formulations

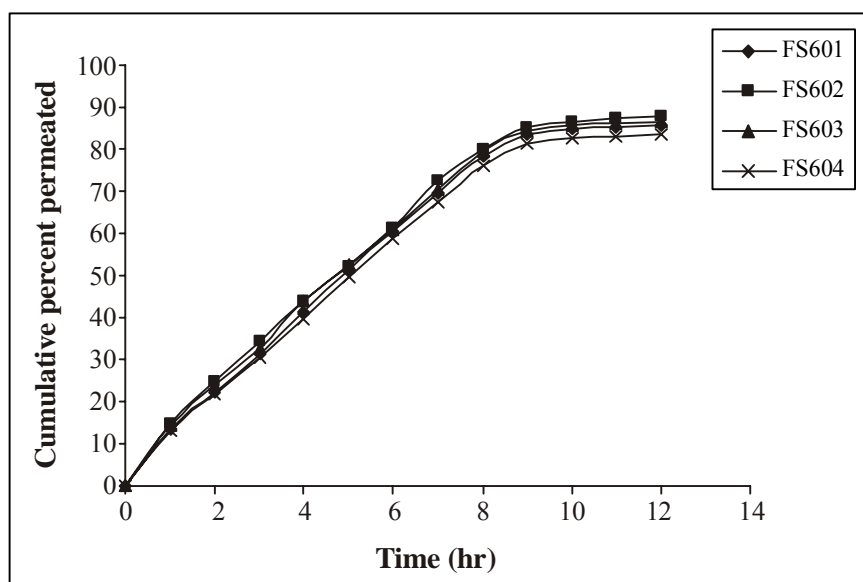


Fig. 2: Release profile of Span 60 niosome formulations

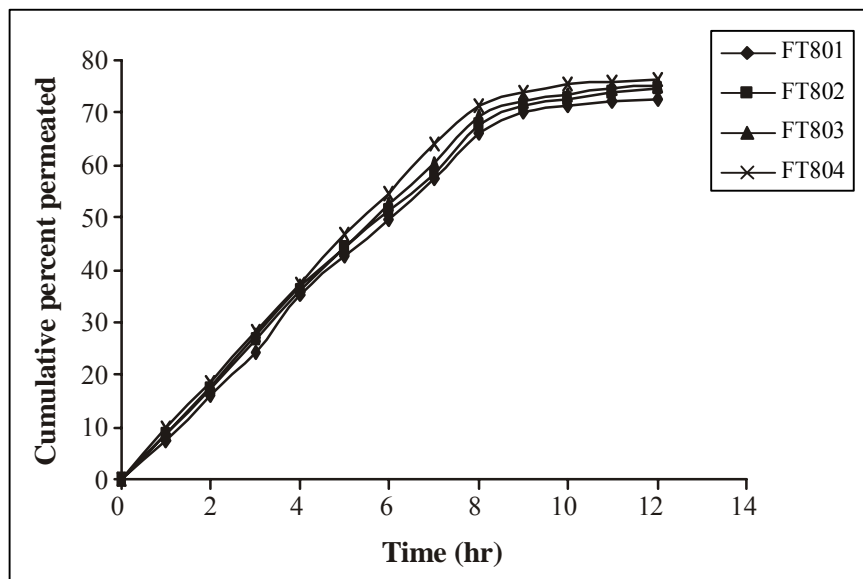


Fig. 3: Release profile of Tween 80 niosome formulations

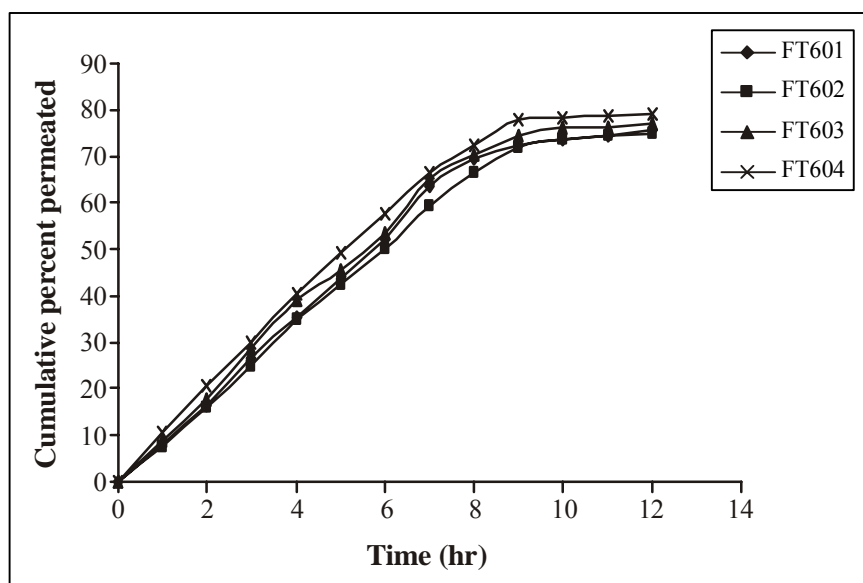


Fig. 4: Release profile of Tween 60 niosome formulations

The entrapment efficiency of niosomes was measured by centrifugation method. The highest and least entrapment of metoprolol tartrate as 89.82 and 63.43 was shown by the

FS60₄ and FT60₄ formulations. The Span groups of surfactants are better in entrapping metoprolol tartrate as compared to Tween group of surfactants. The entrapment efficiency is affected by phase transition temperature of the surfactants. Span 60 is solid at room temperature and showed high phase transition temperature and therefore, exhibits high entrapment efficiency.

The *in vitro* release profile of all formulations was studied using dialysis membrane. The *in vitro* release rate studies revealed that the cumulative percent release was maximum for formulation containing Span 80. This was due to small size of the vesicles and its low transition temperature. The intrinsic unsaturation in oleate in Span 80, responsible for low transition temperature, might have better penetration enhancing ability than stearate in Span 60. The results are shown in Table 1. On the basis of above observations, FS80₄ was selected as best formulation.

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