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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE NIOSOMAL GEL

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ABSTRACT

Self-assembly of non-ionic surfactants into vesicles was first reported in the cosmetic industry. Niosomes are osmotically active and stable, increase the stability of entrapped drug. The present study focuses on enhancement of bioavailability and sustaining the release rate of metoprolol succinate. Metoprolol succinate niosomes were formulated using different ratios of the span and cholesterol. The vesicles were evaluated for the encapsulation efficiency and drug release. The niosomes were characterized for surface morphology and particle size. SEM studies indicated that there was no aggregation and particles existed as separate entities with uniform size distribution. Among the niosomal formulations prepared, formulations B2 and B3 containing cholesterol and span60 in the ratios 1:1 and 1:3 were selected due to high entrapment efficiency (84% for B2 and 80% for B3), high drug release (82.74% for B2 69.52% for B3) and stability. The formulations B2 and B3 were formulated into niosomal gel using different concentrations of Carbopol 934. The gel formulation could sustain the drug release for 24hrs. Niosomes enhance the bioavailability of metoprolol succinate by avoiding the pre-systemic metabolism, and niosomal gels can sustain the release rate of metoprolol succinate and hence are a promising approach for delivery of drug through transdermal route.

KEYWORDS: Metoprolol succinate, niosomes, niosomal gel, prolonged drug release.

INTRODUCTION

Niosomes are a novel and efficient approach for transdermal drug delivery. As a drug delivery device, niosomes are osmotically active and stable, improve the stability of the entrapped drug. Niosomes are non-ionic surfactant vesicles, with microscopic lamellar bilayer structure formed by self-association of hydrated surfactant monomers. They are structurally similar to liposomes but offer several advantages over liposomes. Niosomes can be used as carriers for both amphiphilic and lipophilic drugs.[1] Niosomes are amphiphilic in nature with particle size ranging from 10nm-100nm.[2] Niosomes act as promising vesicles for drug delivery as they act as drug reservoirs.[3] Due to the presence of non-ionic surfactants niosomes are less toxic, non-immunogenic, biodegradable and improve the therapeutic index of drugs.[4] Niosomes improve the performance of drugs by delaying the clearance from circulation.[5,6] Niosomes delay elimination of rapidly metabolizable drugs and thus can function as sustained release systems.[7] Niosomes are preferred over other vesicular systems as they contribute to an aqueous vesicular suspension which improves the patient compliance over other oily formulations. They do not require special storage conditions such as low temperature or inert environment.[7] They are less expensive and are assumed to exhibit higher chemical stability than that of the phospholipids used in the preparation of liposomes. Phospholipids are easily hydrolysed due to the presence of ester bonds.[8]

Metoprolol succinate is β1 cardio selective adrenoreceptor blocking agent. It is used as an anti-hypertensive, anti-anginal and in acute myocardial infarction. It exhibits high water solubility with 50% bioavailability. The biological half-life of metoprolol succinate is 3-7hrs. To improve the bioavailability of the drug and to deliver the drug in a controlled manner transdermal drug delivery system can be used. Incorporation of metoprolol succinate into niosomal vesicles and further formulating the best selected niosomal suspensions into niosomal gel could sustain the drug release in a controlled manner when given through transdermal route.

MATERIALS AND METHODS

Metoprolol succinate was a kind gift sample from Aizant drug research solutions, India. Span 20, span 60, span 80, and cholesterol were obtained from S.D. Fine-Chem. Ltd, India. Carbopol 943 was obtained from NR CHEM, India. Chloroform, Ethanol, Methanol and Isopropanol were obtained from S.D. Fine-Chem. Ltd, India. All the chemicals were of analytical grade.

Preparation of niosomes: Metoprolol succinate niosomes were prepared by thin film hydration technique. Multilamellar niosomes were prepared by thin film hydration technique. Cholesterol and surfactant were dissolved in chloroform: ethanol mixture (1:1 ratio) in a 100ml round bottom flask. The flask was attached to a rotary evaporator (Superfit®, India) immersed in 60˚C water bath and rotated under vacuum.

This process was continued until all the liquid evaporated and a dry thin lipid film was deposited on the walls of the flask. The flask was left in a vacuum desiccator overnight to ensure complete removal of residual solvent.

Metoprolol succinate which was previously dissolved in phosphate buffer pH-7.4 was then added to the dried film and rotated under similar conditions of rotary evaporation for 30minutes till all the lipid film comes into the aqueous buffer resulting in the formation of niosomes. The conversion of the buffer solution into a milky white suspension indicated the formation of niosomes. The flask was removed and niosomes were transferred to a container and subjected to sonication in a bath sonicator for 15minutes with a 5minute pulse. Niosomes were allowed to swell over-night under refrigeration. The niosomal suspension was stored at 4˚C until further analysis.[3,9]

Optimization of lipid concentration: Different concentrations of lipid were taken in round bottom flask along with surfactant in chloroform: ethanol mixture as shown table1.

Table 1: Optimization of Lipid Content.

Lipid Concentration (mg)	Surfactant Concentration (mg)	Solvent Mixture (Chloroform: Ethanol)
100	500	1:1
250		
500		
1000		

EXPERIMENT-I

Formulation of Metoprolol Succinate Niosomes

Niosomes for transdermal delivery were prepared by thin-film hydration method followed by sonication. Span 20, span 60, span 80 were used as surfactants and cholesterol was used as a membrane stabilizer as given in table 2.

Table 2: Formulation of Metoprolol Succinate Niosomes.

Formulation Code	Span (mg)	Cholesterol (mg)
Span 20		
A1	1500	500
A2	500	500
A3	500	1500
Span60		
B1	1500	500
B2	500	500
B3	500	1500
Span80		
C1	1500	500
C2	500	500
C3	500	1500

***Drug content: 25mg, Formulation codes: (A1, A2, A3- span 20);**
(B1, B2, B3-span-60); (C1, C2, C3-span-80)

Figure 1: Formation of Drug Entrapped Niosomes.

Evaluation of Niosomes

Determination of Drug Entrapment Efficiency

Niosomal formulations were centrifuged at 3000 RPM for 30 mins using ultracentrifuge to separate niosomes from unentrapped drug. Concentration of the drug was determined by lysing the pellet using isopropyl alcohol and measuring absorbance at 223 nm using UV spectrophotometer.[10]

$$\text{Entrapment Efficiency} = \frac{\text{Amount of Drug Encapsulated}}{\text{Total Amount of Drug}} \times 100$$

***In-vitro* Drug Release Studies**

In-vitro drug release of niosomal suspension was studied using a Franz diffusion cell. The donor compartment contained 1ml of niosomal suspension and receptor compartment contained phosphate buffer (pH 7.4). The temperature was maintained at 37±1 ˚C and the whole

assembly was stirred using a magnetic stirrer. Samples were withdrawn through the sampling port at pre-determined time intervals for 6 hours and were analysed using UV - visible spectrophotometer at 223nm. An equal volume of fresh phosphate buffer (pH 7.4) was replaced into the receptor compartment after withdrawal of each sample to maintain sink conditions.[11]

CHARACTERIZATION OF NIOSOMES

Surface Morphological Studies

SEM- The morphology of niosomes was determined using scanning electron microscopy (Hitachi-S3700N). SEM gives a three-dimensional image of the globules. One drop of niosomal suspension was mounted on a clear glass stub. It was then air dried and gold coated using sodium auro thiomalate to visualize under scanning electron microscope 10,000 magnification.[12]

Particle Size Measurement And Zeta Potential

The z-average diameter of sonicated vesicles was determined by dynamic light scattering using a particle size analyser (Horiba scientific nanopartica SZ 100). For measurement, 100µl of the formulation was diluted with an appropriate volume of pH 7.4 phosphate buffer and the vesicle diameter and zeta potential were determined.[13]

Stability Studies

The physical stability of the developed niosomes was carried out for 3 months. The best selected formulations were stored at three different temperature ranges for 3-months i.e., refrigerator conditions (4-8±2˚C), room temperature (25±2˚C) and oven temperature (45±2˚C). Samples were observed and evaluated after 90days.

EXPERIMENT-II

Formulation of Niosomal Gel

Metoprolol succinate niosomal gel was formulated by dispersing Carbopol 934 in different concentrations (1.5 % and 2%) to niosomal suspension. The solution was allowed to swell overnight to obtain niosomal gel.

Evaluation of Niosomal Gel

Organoleptic Characteristics

The formulations were tested for organoleptic properties, like colour, odour, texture, phase separation and feel upon application.[14]

pH Measurement

1 gm of gel was dissolved in 30ml of distilled water (pH 7.4). The pH of the Niosomal gel was determined using digital pH-meter by bringing the probe of the pH meter in contact with the solution.[14]

Drug content

One gram of gel was dissolved in 100ml of phosphate buffer pH 7.4, stirred constantly for 2 days using magnetic stirrer, the resultant solution was filtered and content was analysed by U.V Spectrophotometer.[15,16]

In-Vitro Drug Release Studies

In-vitro drug release of Niosomal suspension was studied using a Franz diffusion cell. The donor compartment contained 1g of niosomal gel and receptor compartment contained phosphate buffer (pH 7.4). The whole assembly was maintained at 37 ˚C ±1 ˚C and was stirred using a magnetic stirrer. Samples were withdrawn through the sampling port at pre-determined time intervals for 24 hours and were analysed by UV - visible spectrophotometer at 223nm. An equal volume of fresh phosphate buffer (pH 7.4) was replaced into the receptor compartment after withdrawal of each sample to maintain sink conditions.[17]

RESULTS AND DISCUSSION

In the experimental section, attempts were made to formulate Metoprolol succinate niosomes and niosomal-gel. The formulations were selected based on entrapment efficiency, *invitro* drug release and stability studies.

Optimization of Lipid Concentration: Niosomal vesicles were formulated using different concentration of lipids. The niosomal vesicles formed with 500mg of cholesterol were smooth and uniform in surface and hence were selected for further study.

EVALUATION OF NIOSOMES

Entrapment efficiency: Entrapment efficiency was determined by lysing the niosomal vesicles using isopropanol.

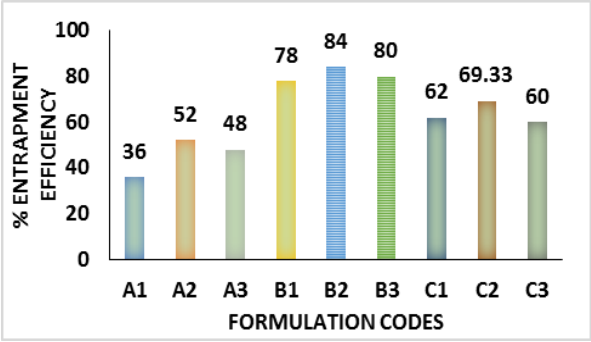

Figure 2: Entrapment Efficiency of Metoprolol Succinate Niosomes.

The entrapment efficiency was found to be higher for the formulations B2 and B3 containing cholesterol : span60 in the ratios 1:1 and 1:3 respectively as seen in figure 2 Hence these ratios were taken as best selected formulations and used for further study. At this concentration cholesterol increases hydrophobicity of the bilayer, and improves stability. The length of the alkyl chain influences the hydrophilic lipophilic balance (HLB value) of the surfactant. Higher the HLB value of the surfactant, the entrapment efficiency of the formulation increases. (HLB- span 20-4.3, span 60-4.7, span 80-4.3). The HLB value of span 60 was higer than span 20 and span 80 and hence, the formulations containing span60 were further studied for drug release.

***In-vitro* drug release studies:** The *in-vitro* drug release of niosomal formulations was determined using Franz diffusion cell. Formulation B2 containing cholesterol and span 60 in the ratio (1:1) released 82.74±1.85 in 6hrs and formulation B3 containing cholesterol and span 60 in the ratio (1:3) released 69.52±2.55 in 6hrs. Hence formulation B2 was taken as best selected formulation.

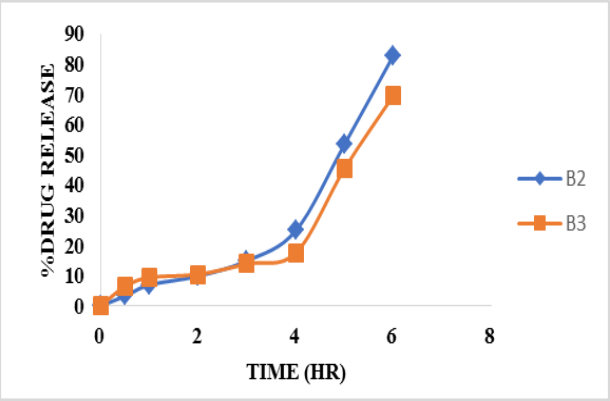

Figure 3: *In-vitro* Drug Release Studies of Metoprolol Succinate Loaded Niosomes.

Optical microscopy: The niosomal suspension was observed under 40x magnification (fig:5). The vesicles appeared to be uniform in size and existed as separate entities with no aggregation.

Surface morphology: The morphology of niosomes was determined using scanning electron microscopy (Hitachi-S3700N). SEM photographs (fig: 4) revealed that particles were uniform in size. The average particle size of the vesicles was found to be 100µm. The niosomes existed as separate entities and there was no aggregation.

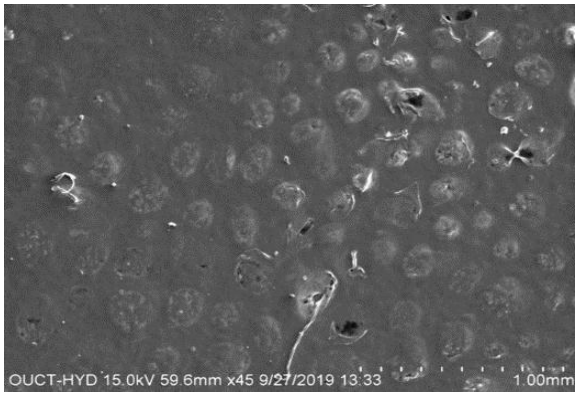

Figure 4: SEM Photographs of Metoprolol Succinate Niosomes.

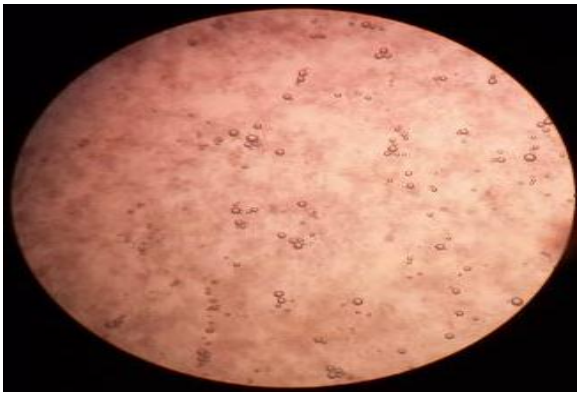

Figure 5: Photograph of Metoprolol Succinate Niosomes in 40× Magnification.

Particle size measurement and zeta potential: The z-average diameter of sonicated vesicles was determined by dynamic light scattering using a particle size analyser (Horiba scientific nanopartica SZ 100).

Poly dispersity index and droplet size: The particles were in the range of 100-1000nm. (fig 6) Polydispersity index was found to be 1.014 and average particle size was found to be 2884.2nm.

Zeta potential: The niosomal formulation had a zeta potential value of -59.2 mV (fig: 7), which is a measure of net charge of the niosomes. This higher charge on the surface of vesicles produced a repulsive force between the vesicles which made them stable and devoid of agglomeration and faster settling, providing an evenly distributed suspension. It can be concluded that the niosomal formulations show good stability and hence were processed for formulation of gel.

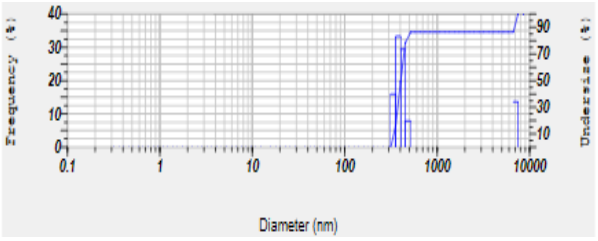

Figure 6: Statistical Bar Graph of Particle Size Distribution In Niosomal Suspension.

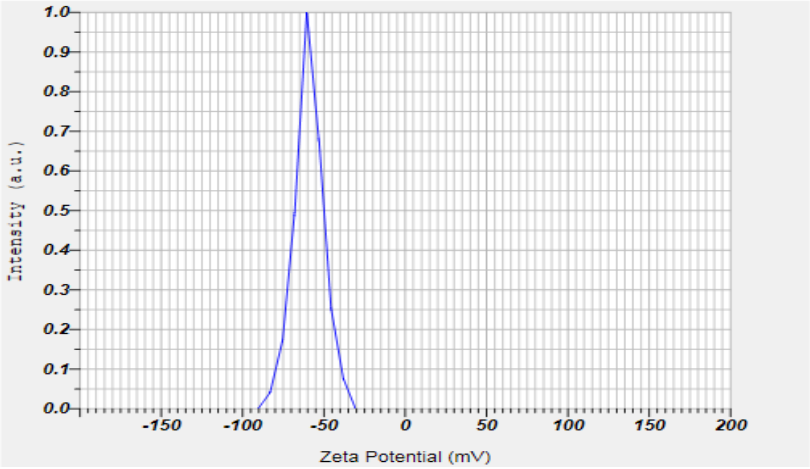

Figure 7: Zeta potential of Niosomal Suspension.

Table 3: Stability Behaviour of Colloid as Per Zeta Potential.

Zeta potential (mV)	Stability Behaviour of Colloid
From 0 to ± 5	Rapid Coagulation or Flocculation.
From 10 to ± 30	Incipient Instability
From 30 to ± 40	Moderate Stability
From 40 to ± 60	Good Stability
> ± 61	Excellent Stability

Stability studies: Stability studies of the niosomal suspensions were carried out for 3 months at three different temperature conditions i.e., refrigeration temperature (4-8˚C), room temperature (25±2˚C) and oven temperature (45±2˚C). The drug content of niosomal suspensions after 12 weeks is shown in table 4.

Table 4: Stability Conditions of Formulated Metoprolol Succinate Niosomes.

Parameter	Storage Conditions	3 Months
Drug content	4-8±3˚C	93.97%
	25±2˚C	95.02%
	45±2˚C	75.48%

The niosomal formulation stored at refrigeration and room temperatures did not show significant difference in percentage drug content, the formulations stored at oven temperature showed reduced percentage drug content reduced. Hence, refrigeration and room temperature were considered as optimal temperature for storage of niosomes.

Evaluation of Niosomal Gel

Organoleptic characteristics: The organoleptic characteristics of the niosomal formulations were determined by visual examination. All the formulations were opaque, white in colour, odourless, had a smooth appearance.

pH: pH of the niosomal formulations was determined using a digital pH meter, pH of all the formulations was in the range of 6.9-7.5. The pH of the best selected formulation (B2) was found to be 7.0. hence the preparation would be non-irritating when applied on the skin.

Drug content: The drug content of the niosomal formulation was determined using UV-visible spectrophotometer. The percentage drug content of formulations B2 and B3 is given in table 5.

Table 5: Drug Content In Formulated Metoprolol Succinate Niosomes.

Formulation Code	% Drug Content
B2	92.56±1.12
B3	85±1.06

***In-vitro* drug release:** The *in-vitro* drug release of the niosomal gel was carried out using Franz diffusion cell.

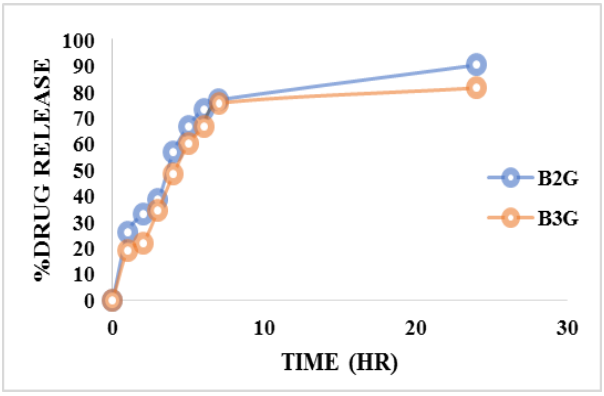

Figure 8: *In-vitro* Drug Release Studies of Metoprolol Succinate Loaded Niosomes.

Formulation B2G containing Carbopol 934 (1.5%) released 90.22% in 24hrs and formulation B3G containing Carbopol 934 (2%) released 81.4% in 24hrs.

Hence formulation B2G was taken as best selected formulation.

Comparing the 6hr data the niosomal formulation B2 exhibited drug release of 82.74% while the niosomal gel formulation could release 73.36% for 6hrs, this is because the gel formulations provide higher diffusional resistance for drug release. The higher permeability of drug through skin is because of presence of colloidal carriers. Hence, the niosomal gel could sustain the release of the drug for 24hrs.

CONCLUSIONS

The formulation of metoprolol succinate niosomal gel using Carbopol 934 prolonged the drug release of metoprolol succinate due to the presence of colloidal carriers. On the basis of the results we can conclude that niosomal gel is a promising drug delivery system to deliver metoprolol succinate transdermally to prolong the drug release and it can be further studied for *in-vivo* release characteristics.

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