FORMULATION AND EVALUATION OF NIOSOMAL DRUG DELIVERY OF α -LIPOIC ACID

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ABSTRACT

The present study is an aim to overall improvement in the efficacy, reduced toxicity and enhancement of therapeutic index of niosome carrying α-lipoic acid. Niosome were prepared by hand shaking method using span and tween (20 and/or 60). The preparations were characterize with respect to size reduction, entrapment efficiency, *in-vitro* drug release profile and stability under specific conditions. The diameter of niosomes ranges from 1-4μm with spherical/oval in shape. The entrapment efficiency of the vesicles was found to be 66.99%, 71.03%, 73.58% and 68.41% for F1, F2, F3 and F4 respectively. Highly cumulative release was observed with 61.29% for span-20, 63.72% for span-60, 79.44 % for tween-20 and 81.51 % for tween-60 respectively. Stability studies proved that optimum storage condition for niosomes was found to be 4°c.

KEY WORDS: Niosomes, α-Lipoic acid, Span and Tween (20 and/or 60).

1.INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery (Li,1987). Niosomes or non ionic surfactant vesicles are microscopic lamellar structures form from the mixture of non-ionic surfactant, cholesterol and dicetyl media (Malhotra and Jain,1994). Niosomes can entrap solutes in a manner analogous to liposomes. They are stable *in-vitro* and can increases the stability of the entrapped drugs (Hofland,1992). Niosomes are biodegradable, biocompatible and non-immunogenic in nature and exhibit flexibility in their structure characterization (Azmin,1985). α-lipoic acid is a fatty acid found naturally inside every cell in the body. It converts glucose into energy and neutralizes free radicals. It can damage cells and contribute to aging and chronic illness (Henriksen,2006). Hence, the present study is to design drug delivery of α-lipoic acid in the form of therapeutic index.

2.MATERIALS AND METHODS

Chemicals and Reagents:

Cholesterol (Loba Chemicals Pvt. Ltd, Mumbai), Span and Tween having grades 20 and 60 respectively (Hi-media Chemicals Pvt. Ltd., Mumbai and Ranbaxy Fine Chemical Ltd., New Delhi), α-Lipoic acid (Dr. Reddy Laboratories, Hyderabad). All other reagents used for the study were of analytical grade.

Formulation of Niosomes:

Non-ionic surfactant (Niosomes) of α-lipoic acid was prepared by hand shaking method. The calculated quantity of surfactant was dissolved in 2 ml of chloroform methanol mixture (1:1) and the solvent was evaporated at room temperature using a rotary evaporator. The thin layer of solid mixture deposited on the wall of round bottomed flask was hydrated with the phosphate buffer with PH 7.4 at 7°c for 15 minute. This suspension was

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then sonicated for 3x30 seconds to form unialamellar vesicles (Rajg,1994).

Evaluation of Niosomes:

Entrapment efficiency:

After preparing niosomal dispersion, unentrapped drug is separated by dialysis (Chauhan and Lawrence,1989), centrifugation (Yoshioka,1994;Gayatri Devi,2000) and gel filtration (Szoka,1980). The drug remain entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation.

$$\text{Entrapment effeciency} = \frac{\text{Amount of entraped drug}}{\text{Amount of total drug}} \times 100$$

Particle size analysis:

Particle size analysis was done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs were placed briefly in a drier and then coated with gold in an ion sputter. Pictures of niosomes were taken by random scanning of the stub and count it as showing in Table 2. The diameter is about 30 niosomes was measured from the photomicrographs of each batch. Finally, average mean diameters were taken into consideration (Sattuwar,2001;Balasubramanium,2002).

***In-vitro* release study:**

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm^2 area. Trimmed away the excess fat and sliced to 500 µm thickness using a Daw's derma tone (Yoshioka,1994). These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C., filled with 100 ml of PBS) and add 10 mg niosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37 ± 0.5°C and stirred magnetically at 50 r.p.m., aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by U. V. Spectrophotometer method at 294 nm (Shahiwala and Mishra,2002).

Stability study:

All niosomal formulations were subjected to stability studies by storering at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations were checked by method discussed previously in entrapped efficiency parameter. *In-vitro* release studies of selected formulations were also carried out (Doijad,2008).

3.RESULTS AND DISCUSSION

Niosomes of α-lipoic acid were prepared by Hand shaking method, four batches (F1, F2, F3 and F4) of niosomes formulations showing in Table 1 and characterize with respect to size reduction (Table 2), the maximum number of niosomes were found in size range 3-4µm of span-20 (58), 1-4µm tween-60 (58), 1-3µm span-60 (51) and 1-3µm tween-20 (58). The percent entrapment efficiency (Table 3), found more than 50% such as 66.99%, 71.03%, 73.58% and 68.41% for F1, F2, F3 and F4 respectively. *In-vitro* drug release profile (Fig. 1), the cumulative percentage release of pure drug was observed 98.38 at 5 hrs and formulated niosomes 61.29%, 63.72%, 79.44% and 81.51% for span-20, span-60, tween-20 and tween-60 respectively after 24 hrs. Formulated niosomes showed interesting biphasic release with an initial burst effect. Drug released 11.78, 12.66, 14.54 and 14.92 for F1, F2, F3 and F4 respectively at in 1 hr. The mechanism for the burst released in the 1 hr can be attributed to the drug loaded on the niosomes surface and imperfect entrapment of drug by the vesicles. Average particle sizes of non-ionic surface vesicles of niosomes were scanned (Fig. 2) at 1-3 µm and spherical/oval in shape. The stability study revealed that, there is no significant change in drug content after storage for three months at 4°C, 25°C and 37°C. *In-vitro* release stability study showed, at 4°C released 94.95 %, at 25°C released 91% and at 37°C released 81.17% after 12 hrs. The drug released from the formulation stored at 4°C was highest followed by the formulation stored at 25°C and 37°C. This may be attributing to phase transition of surfactants and lipid causing vesicle leakage at higher temperature during storage, Hence, from the data, the optimum storage condition for the α-lipoic acid niosome was found to be 4°C. Non-ionic surfactant with cholesterol is a suitable carrier for the preparation of niosomes of α-lipoic acid. Span-60 showed maximum entrapment efficiency, which can be attributed to high lipophilicity of the surfactant. Prepared niosomes followed peppas diffusion controlled release mechanism. The targeted efficiency of drug loaded niosomes was higher as compared to the pure drug α-lipoic acid which may provide increased

therapeutic efficacy. However, higher concentration of drug targeted to various sites may help in the reduction of dose required for therapy and thereby dose related systemic side effects too. On the basis of drug content, particle size morphology, *in-vitro* release and stability studies, it can be concluded that, formulation prepared from tween-60 was an optimum formulation. Thus, further detailed investigation need to carryout to establish efficiency of this formulation.

Table 1: Batches of formulations of α-lipoic acid niosomes

Ingredients (Mg/ml)	Formulations			
	F1	F2	F3	F4
α-Lipoic Acid	10	10	10	10
Span-20	25	-	-	-
Span-60	-	25	-	-
Tween-20	-	-	25	-
Tween-60	-	-	-	25
Cholesterol	25	25	25	25
Chloroform	2	2	2	2
Ether	8	8	8	8

Table 2: Characterization of a-lipoic acid niosomes with respect to size reduction

Size range (μm)	Number of Niosomes			
	Span-20	Span-60	Tween-20	Tween-60
1-3	55	51	58	58
3-4	58	50	56	58
4-5	12	24	11	09

Table 3: Characterization of α-lipoic acid niosomes with respect to % entrapment efficiency

Formulations	PEE ± SD
F1	66.99 ± 0.45
F2	71.03 ± 0.32
F3	73.58 ± 0.19
F4	68.41 ± 0.12

Where, PEE: Percent Entrapment Efficiency, SD: Standard Deviation

Figure 1: *In-vitro* release profile of α-lipoic acid niosomes formulations

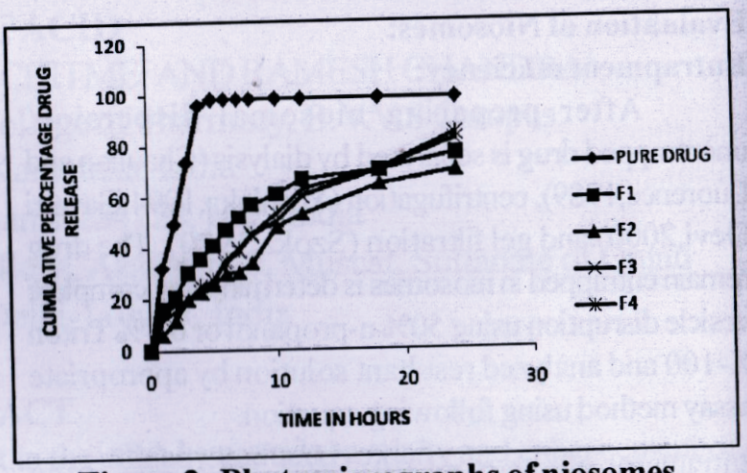
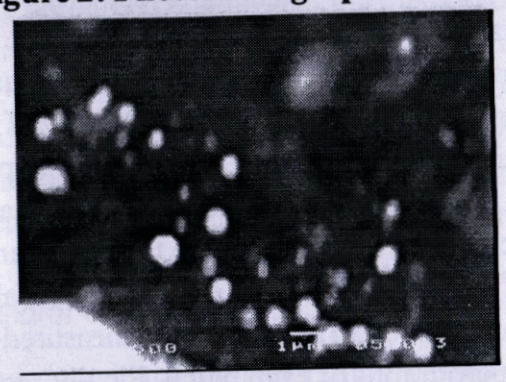


Figure 2: Photomicrographs of niosomes



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