Research Article

Proniosomes Formulations Using Maltodextrin and Mannitol as Carriers

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ABSTRACT
Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic and hydrophilic drugs. Maltodextrin and Mannitol has been used as carriers for the preparation of Various Proniosome powder formulations by slurry method. Niosomes derived from Proniosomes of both carriers were compared in terms of morphology, vesicle size, entrapment efficiency and in vitro drug release.Ketorolac Tromethamine used as model drug. Average particle was found to be in range of 3.06 to 12.60 µm for Maltodextrin and from 3.39-4.62 µm for Mannitol. Percentage cumulative drug release was less in Mannitol as compared to Maltodextrin while entrapment efficiency was higher in Mannitol as compared to Maltodextrin.Thus it can be concluded that Mannitol can be used as suitable carrier for preparation of proniosomes.

Keywords: Proniosomes, Niosomes, Maltodextrin, Mannitol.

1. INTRODUCTION

Colloid (Gr., - glue like), a mixture in which one substance is divided into minute particles (called colloidal particles) and dispersed throughout a second substance. The mixture is also called as colloidal solution, or colloidal dispersion e.g. liposome or niosomes.Such type of carrier system have distinct advantages over conventional dosage forms carriers, they act as drug reservoirs and protect the drug from premature degradation, modification of particle composition and surface can adjust the drug release and these particles have affinity to target the site.[1]

Liposomes are broadly defined as lipid bilayers surrounding an aqueous space. They are unilamellar or multilamellar spheroid structures which can be used for hydrophobic and lipophilic drugs that can partition into the lipid phase and unilamellar vesicles can be used to entrap water soluble drugs in interior aqueous space[2]. Liposomes have been investigated for their potentional application in pharmaceutics; such as drug delivery, targeting, controlled release or increase of solubility[3]. Niosomes are similar systems in which non-ionic surfactants are used instead of phospholipids. The low cost, greater stability and resultant ease of storage of non-ionic surfactant has led to the exploitation of those compounds as alternatives to phospholipids. Even though niosomes exhibit good chemical stability during storage, there may be problems of physical instability in niosomal dispersion. Like liposomes, aqueous suspensions of niosomes may exhibit aggregation, fusion, leaking of entrapped drugs, or hydrolysis of encapsulated drugs, thus limiting the shelf life of the dispersion.[4]

The traditional method for producing niosomes or liposomes methods are time consuming and may involve specialized equipment. The thin film approach allows only for a predetermined lot size so material is often wasted if smaller quantities are required for a particular application or dose[2].

Proniosomes circumvent all of these problems. These are dry formulations of surfactant-coated carrier which can be hydrated by brief agitation in hot water for a short period of time. This dry product, which could be hydrated immediately before use, would avoid many of problems associated with aqueous niosomes dispersion and problems of physical stability (aggregation, fusion, leaking) could be minimized. The additional convenience of the transportation, distribution, storage and dosing makes ‘dry niosomes’ a promising industrial product. This dry, free flowing granular product which, upon addition of water, disperse or

dissolves to form a multilamellar noisome suspension suitable for administration by oral or other routes.

The present work is aimed to prepare Proniosomes (dry niosomes) using Ketorolac Tromethamine (KT).Ketorolac Tromethamine is nonsteroidal agent with potent analgesic and moderate anti-inflammatory activity .Mannitol and Maltodextrin are used as carriers and evaluate proniosomes/niosomes derived from proniosomes with respect to morphology, entrapment efficiency, *in vitro* release and stability.

2 MATERIALS AND METHODS

Cholesterol was purchased from Lobachemie, Dioctylsodium sulphosuccinate from CDH Pvt. Ltd., New Delhi, Span 60 from SD fine- Chem. Ltd. Mumbai, Diethyl ether from Qualigens fine Chemicals, Mumbai, Maltodextrin from Himedia Lab. Ltd., Mumbai, Mannitol from Qualigens fine Chemicals, Mumbai,Disodium Hydrogen Phosphate from Qualigens fine Chemicals, Mumbai, Sodium Dihydrogen Phosphate from Qualigens fine Chemicals, Mumbai, Sodium Chloride from Qualigens fine Chemicals, Mumbai, Acetonitrile from Qualigens fine Chemicals, Mumbai ,and Triton X 100 from Qualigens fine Chemicals, Mumbai. The drug ketorolac tromethamine was obtained as gift sample from Ranbaxy Laboratory Ltd., Gurgaon.

2.1 Preparation of Proniosomes

Proniosomes based on maltodextrin[7] and mannitol[8] as carrier were prepared by slurry method using Span 60, Cholesterol and Dioctylsodiumsulphonsuccinate (DOSS) in molar proportions of 47.5: 47.5:5 respectively, A stock solution containing 164 mmol/L of Span 60[9], 164 mmol/L of cholesterol[6] and 17.2 mmol/L of dioctylsodium sulphosuccinate[10] was prepared in diethyl ether. One gram of carrier powder was taken in the 50 ml round bottom flask. To this calculated amount of surfactant stock solution was added. The flask was attached to rotary evaporator and rotated at 100 rpm, and temperature was maintained at 35°C by water bath. The flask was rotated until the powder appeared to be dry and free flowing. The flask was removed and kept overnight in a dessicator. Proniosome powder so obtained was stored in a sealed container. Proniosome powder (prepared as described above) was weighed and water or aqueous drug solution at 80°C was added to it in a volumetric flask. The preparation was vortexed at maximum setting for 2 minutes to prepare niosomal suspension[4]. Niosomes suspensions were prepared such that the total surfactant concentration was the same, this required hydration of different amounts of proniosomes depending on the surfactant loading as shown in table 1.

2.2 Scanning electron microscopy

Proniosome, prepared as described above were sprinkled on double sided conductive carbon tape on an aluminum stub. Excess sample was blown off with compressed air. The specimen was then coated with Au/Pd (60/40), using a ladd sputter coater at 2.5 KV and 20 mA for 45s. The coated specimen was observed using Leo 435 VP scanning electron microscope at 30 KV.

2.3 Transmission electron microscopy

The morphology of hydrated niosome dispersion prepared from proniosome was also determined using transmission electron microscope. A drop of niosome dispersion was applied to a carbon-coated 300 mesh copper grid and left for 1 minute to allow some of the niosomes to adhere to the carbon substrate. The remaining dispersion was removed by absorbing the drop with the corner of a piece of filter paper. A drop of 2% aqueous solution of uranyl acetate was applied for 35s. The remaining solution was removed by absorbing the liquid with the tip of a piece of filter paper and the sample was air dried. The sample was observed with a Fei-Philips morgagni 268D transmission electron microscope at 100 KV.

2.4 In vitro drug release

The in vitro drug release from niosomal suspension was determined by using everted chick ileum method. The fresh intestine was brought from local butcher's shop and kept in tyrode solution[12]. After discarding approximately a 10-15 cm section from the pyloric end, the entire intestine was everted, using a blunt headed glass rod. The everted gut was stretched under a weight of 10 gm and cut into 10 cm segments. A segment prepared in this manner was ligated at the distal end and attached at the proximal end to the cannulated end of tube E. A weight of 10 gm was attached to the ligated end to keep the sac in a vertical position. The segment was suspended in tyrode solution. The drug containing solution was pre-equilibrated at 37°C and was maintained at that temperature during the experiment. The drug containing solution was referred to as mucosal solution. A 2 ml aliquot of drug free buffer, also pre-equilibrated at 37°C and referred to as serosal solutions was introduced into the sac via tube E.A. 95: 5 mixture of O_2/CO_2 was continuously bubbled through the mucosal solution at a

constant rate. The serosal solution was withdrawn after each hour and replaced with fresh, drug free buffer[13]. The concentration of the drug in serosal fluid samples was analyzed using UV method.

2.5 Entrapment efficiency

For determining the entrapment efficiency 'free' or 'unentrapped' drug was separated from niosomal dispersion by filtering through membrane filter (0.2 um). The filtrate was analyzed for free drug by HPLC method. The concentration obtained was subtracted from total drug concentration to get entrapment efficiency.

3. RESULT AND DISCUSSION

3.1 Particle size distribution

Particle size analysis of niosome preparations showed that niosomes based on maltodextrin were larger and slightly more heterogeneous than those of mannitol based.

Although the size distributions were approximately the same, the average particle size of maltodextrin niosomes were in the range of 3.6-12.5µm as in fig 1

3.2 Entrapment efficiency

Drug entrapment was measured by filtration method, in which the unentrapped drug was assayed by HPLC and the entrapped drug determined by difference. For niosomes derived from maltodextrin based proniosomes entrapment efficiency of ketorolac tromethamine was found to be 79-86% (Table2) while in case of niosomes derived from mannitol based proniosomes, ketorolac was found to be 87-97% entrapped within niosomes(Table2). Higher entrapment in case of mannitol based niosomes may be because of thinner surfactant film on mannitol surface.

3.3 *In Vitro* Release

To study the effect of carrier on *In vitro* release rate of ketorolac tromethamine from proniosomes an everted chick ileum preparation was used. The results of 5 hr. *in vitro* released study through everted chick ileum preparation. The results reveal that 5 hr. percentage cumulative release from niosomes derived from maltodextrin based proniosomes was more than niosomes derived from mannitol based proniosomes. *In vitro* release was also found to decrease with increased surfactant loading. Smaller release rate in case of mannitol may be because of higher entrapment efficiency, more stabilized niosomal membrane and due to osmotic effect of mannitol. Decrease release rate with increased surfactant loading may because of thicker and more stabilized niosomal membrane.

4. CONCLUSION

Proniosomes consist of dry, free flowing powder which on hydration forms multilamellar niosomal suspension, suitable for administration by oral and other routes. Sorbitol (HU & Rhodes 1999) and maltodextrin (Welsh & Rhodes 2001) have been used as carriers for proniosomes. In the present investigation proniosomes were prepared using mannitol as a carrier and compared with maltodextrin based proniosomes. Ketorolac tromethamine was used a model drug. Proniosomes of mannitol and maltodextrin were prepared by slurry method. Niosomes were prepared from proniosomes by hydrating proniosome powder. Niosomes, so obtained were characterized for morphology, entrapment efficiency and in vitro release and drug stability. SEM of coated and uncoated MTL and MDX indicates that MDX is covered by a thick layer or surfactant while MTL proniosomes show a thin covering of surfactant. Average particle was found to be in range of 3.06 to 12.60 µm for MDX and from 3.39-4.62 µm for MTL. Percentage cumulative drug release was less in MTL as compared to MDX while entrapment efficiency was higher in MTL as compared to MDX.

So it can be concluded that mannitol can also be used as suitable carrier for the preparation of proniosomes.

Table 1: Relative proportions of Span60, Cholesterol, DOSS and carrier with different surfactant loadings

Preparation	Span 60 % (w/w)	Cholesterol % (w/w)	DOSS % (w/w)	Carrier % (w/w)
1X	8.4	7.6	1.0	83.0
2X	14.5	13.0	1.6	70.9
4X	22.5	20.2	2.4	54.9
8X	31.0	27.8	3.4	37.8
16X	38.2	34.3	4.2	23.3
32X	43.3	38.8	4.7	13.2
64X	46.3	41.6	5.0	7.1

Table 2: Entrapment efficiency of MDX and MTL based proniosomes

S. No.	Surfactant Loading	Entrapment Efficiency (MDX)	Entrapment Efficiency (MTL)
1.	1X	87	79
2.	2X	97	84
3.	4X	89	86
4.	8X	89	86.4
5.	16X	87.7	85.6
6.	32X	88	86
7.	64X	89	85.6

Table 3: Comparison of %Cumulative drug release of MDX & MTL

S. No.	Surfactant Loading	% Cumulative drug release	
		MDX	MTL
1.	1X	59.6	56.7
2.	2X	52.7	47.6
3.	8X	43.9	38.6
4.	32X	35.3	32.8

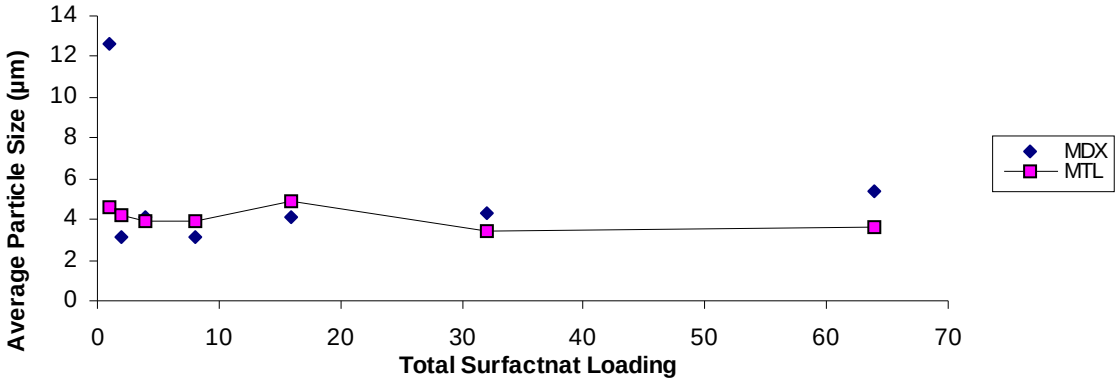

Fig. 1: Particle size distribution

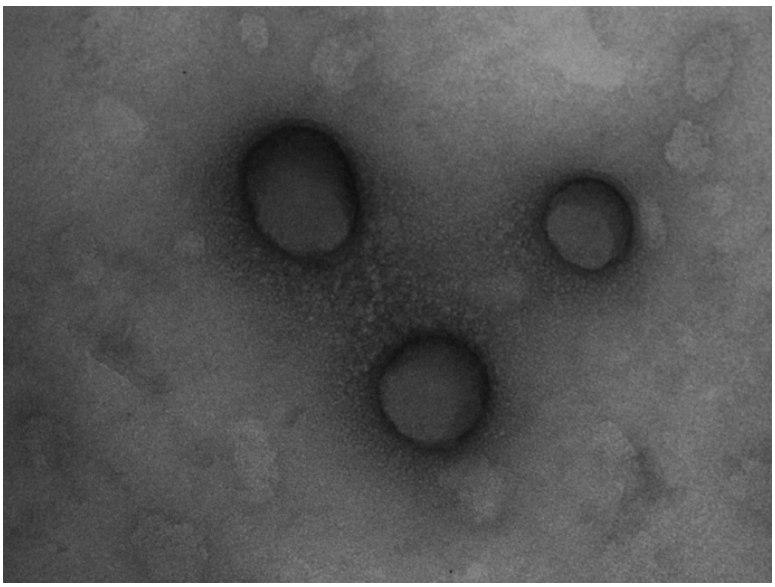

Fig. 2: TEM of niosomal dispersion of Maltodextrin

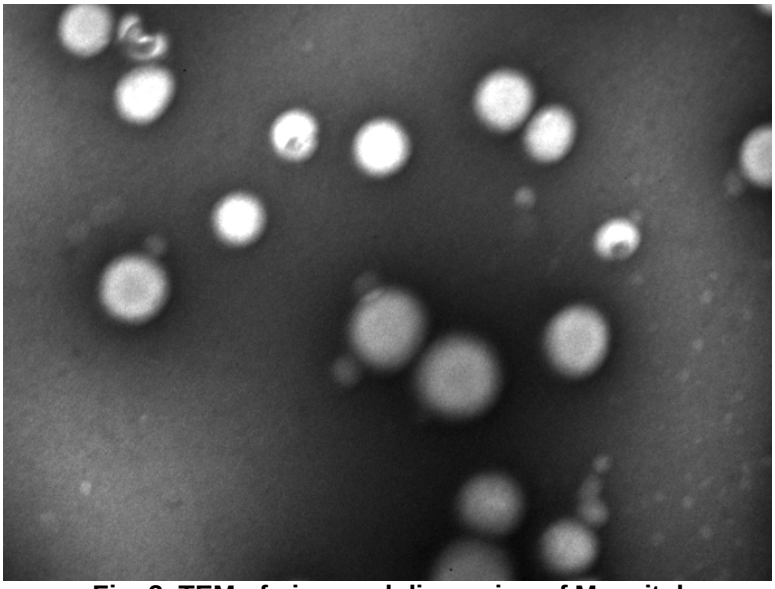

Fig. 3: TEM of niosomal dispersion of Mannitol

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