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Proniosomal Powder of Captopril: Formulation and Evaluation

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Abstract: The aim of the present study was to design a proniosomal drug delivery system of captopril to overcome the limitations of conventional dosage form and to optimize encapsulation parameters to achieve a delivery system suitable for in vitro investigations. Proniosomes are dry powders, which makes richer processing and packing possible. A surfactant coated carrier method was utilized to formulate proniosomal powder containing captopril as a model drug. This system was evaluated in vitro for drug loading, vesicle size, angle of repose, encapsulation efficiency, and stability studies. This method of proniosome loading resulted in 54.16−70.10% of encapsulation. This study examined critical parameters such as type and composition of surfactant. Proniosomes were investigated by transmission electron microscopy for characterization. Four week stability data for proniosomal powder is reported, and at all sampling points significantly higher drug retention was observed. Thus, it can be concluded that the encapsulation of captopril in proniosomes facilitates the controlled release and constitutes a good choice.

Keywords: Niosomes; proniosomes; captopril; sorbitol

Introduction

Niosomes are unilamellar or multilamellar vesicles formed on admixture of a nonionic surfactant, cholesterol, and phospholipid with subsequent hydration in aqueous medium.[1] Proniosomes are the dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. Proniosomes are normally prepared by spraying surfactant in organic solvent onto sorbitol powder and then evaporating the solvent.[2] These proniosomes minimize the problems of physical stability of niosomes such as aggregation, fusion, and leaking. Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport, and dosing.[3]

Captopril is an orally effective angiotensin-I converting enzyme inhibitor and is used in the treatment of hypertension and congestive heart failure. Captopril has a relatively short elimination half-life in plasma with estimates in humans ranging from 1.6 to 1.9 h.[4] The drug is considered as a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity.[5] Approximately 70% of the ingested oral dose is absorbed in healthy fasting human subjects with an absolute bioavailability of 60%, compared to iv dose.[6] Captopril, which is freely water soluble, is usually prescribed to patient who are chronically ill and require long-term use

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for its therapeutic benefits. Development of a once daily captopril oral formulation would be a significant advantage for patient compliance, accompanied by minimization of drug side effects as a result of reduction of drug blood concentration fluctuations in long term therapy.[7] Different attempts have been made to design long acting devices in the form of sustained or controlled release preparations to deliver a druglike coated tablet, beadlets, hydrophobic tablets, a pulsatile delivery system, microcapsules, a bioadhesive system, floating tablets, and capsules. Hydrophobic tablets showed that the release pattern of captopril complied with the desired zero-order kinetics for controlled release formulation, but the release period was comparatively short. This is the same situation with captopril bead formulation. Even in floating tablets in vitro sustained release was up to 8 h, which is short. Moreover, gastric retention of these systems depends on gastric motility, pH, and the presence of food.[8] The prepared proniosomal formulations follow zero-order kinetics, and release was extended up to 24 h.

The present scenario is full of opportunities. In this regard, there has been substantial progress in the design and development of particulate carriers like proniosomes. These carriers can be modified in term of their size, shape, and type of composition.

Proniosomal powders were characterized for their vesicle size, angle of repose, entrapment efficiency, drug release, and stability studies. Various formulations of proniosomal powder were studied to obtain proniosomes of desired attributes. Thus formulation of proniosomes is a practical and simple method of producing niosomes at the point of use for drug delivery.

Experimental Section

Materials. Captopril (Promed, New Delhi), soya lecithin (Himedia, Mumbai), cholesterol (Qualigens, Mumbai), spans (CDH, Delhi), chloroform (Merck, Mumbai), and sorbitol (Loba Chemicals, Mumbai) were purchased. All other ingredients used in the study were of analytical grade.

Development of Proniosomal Powder Formulation. Proniosomal powder was prepared by the method reported by Hu, C., and Rhodes, D. G.[3] A 250 mL round bottomed flask containing 1 g of sorbitol powder was attached to a rotary evaporator. The surfactant and drug mixture was prepared in chloroform. The solution was introduced into the round-bottom flask on the rotary evaporator by sequential spraying of aliquots onto the surface of sorbitol powder. During spraying period the rate of application was controlled so that the powder bed of sorbitol did not become overly wet (such that a slurry would form). The evaporator was then evacuated and the rotating flask was lowered into the water bath at 65−70 °C. The flask was rotated in the water bath under vacuum for 15−20 min or until sorbitol appeared to be dry, and another aliquot of surfactant solution was introduced. This process was repeated until all the surfactant solution had been applied. After addition of the final aliquot, evaporation was continued until the powder was completely dry (about 20−30 min). The material was further dried in desiccator under vacuum at room temperature overnight. This dry preparation is referred as proniosomal powder.

Vesicle Size Analysis. Proniosome-derived niosome dispersion was obtained by hydrating the proniosome powder preparation with 80 °C water and vortexed for 2 min. The resulting niosome dispersion was observed under optical microscope (Olympus, New Delhi) at 100× magnification. Size of 200−300 vesicles was noted using a calibrated ocular and stage micrometer (Erma, Tokyo) fitted in an Optical microscope.

Angle of Repose. The angle of repose of dry proniosome powder was measured by a funnel method.[3] The proniosomal powder was poured into a funnel, which was fixed at a position so that the 13 mm outlet orifice of the funnel was 10 cm above the surface level. The powder flowed down from the funnel to form a cone on the surface, and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Encapsulation Efficiency. To evaluate the loading capacity of proniosomal systems for Captopril, proniosomal powder (100 mg) was hydrated in 80 °C distilled water and vortexed for 2 min. The niosome dispersion so obtained was centrifuged at 18 000 rpm for 40 min at 5 °C (Remi CPR-24 centrifuge).[9] The clear fraction was used for the determination of free drug at 212 nm spectrophotometrically (Shimadzu-1700). The percentage encapsulation efficiency was calculated by using formula

$$\% \text{ encapsulation efficiency} = [1 - (\text{unencapsulated drug/total drug})] \times 100$$

In Vitro Drug Release Studies of Proniosomal Powder Formulation. After the separation of free drug by centrifugation, to the weighed amount of stiff floating fraction of niosomes, 1 mL of phosphate buffer saline was added and vortexed for 10 s to prepare the dispersion. This niosomal dispersion was placed in dialysis cellophane tubing (MMCO14KDC). One end of this tubing was sealed with a plastic clip and other end with a metal clip (to sink the bag). The bag was suspended in a 250 mL beaker containing 200 mL of phosphate buffer pH 7.4 kept at a constant agitation of 600 rpm by using a magnetic stirrer. The temperature of the medium was maintained at 37 °C by a thermostatic

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Table 1. Composition of Proniosomal Powder Formulations

sample no.	formulation code[a]	surfactant type	ratio (mg)	lecithin (mg)	cholesterol (mg)	observation
1	AGD1	S20:S40	500:500	100	100	fine to free flowing powder
2	AGD2	S20:S60	500:500	100	100	fine to free flowing powder
3	AGD3	S20:S65	500:500	100	100	fine to free flowing powder
4	AGD4	S40:S60	500:500	100	100	fine to free flowing powder
5	AGD5	S60:S80	500:500	100	100	fine to free flowing powder

[a] Drug concentration used was 10 mg in each formulation.

Table 2. Vesicle Size Analysis and Encapsulation Efficiency of Selected Proniosomal Powders

sample no.	formulation code	av vesicle size (μm)	% drug loading
1	AGD1	3.14 ± 0.98	60.34 ± 1.36
2	AGD2	2.63 ± 0.47	68.05 ± 1.55
3	AGD3	3.17 ± 0.99	54.42 ± 1.13
4	AGD4	4.98 ± 0.48	70.10 ± 1.28
5	AGD5	1.68 ± 0.51	58.42 ± 1.00

control available on the magnetic stirrer. Aliquots were withdrawn and replaced with the same volume of fresh buffer, at each sampling point. The samples withdrawn were analyzed for the drug content at 212 nm spectrophotometrically.

Stability Studies. The ability of vesicles to retain the drug (drug retention behavior) was assessed by keeping the proniosomal powder formulations at three different temperature conditions, i.e., refrigeration temperature (4−8 °C), room temperature (25 ± 2 °C), and oven (45 ± 2 °C).[10] Throughout the study, proniosomal formulations were stored in aluminum foil sealed glass vials. The samples were withdrawn at different time points during 1 month, and drug leakage from the formulations was analyzed for the drug content spectrophotometrically.

Results

Experiments were designed to incorporate captopril into proniosomes using a surfactant coating method, by changing the HLB (hydrophilic−lipophilic balance) using a series of spans, keeping the concentration of cholesterol and lecithin the same as shown in Table 1. Prepared niosomes were analyzed for percent drug entrapment, and results were recorded in Table 2. Entrapment efficiencies of AGD4 and AGD2 were found to be 70.10% and 68.05%, respectively. This might be attributed to the fact that span 40 and span 60 are solid at room temperature and showed a higher phase transition temperature [Tc].[11] Entrapment efficiency of AGD5 was much less than for the others. Span 60 and span 80 have the same head group, but span 80 has an unsaturated alkyl chain. Introduction of a double chain into the paraffin chains causes a marked enhancement in the permeability.[12] This might be the reason for the lower entrapment efficiency of the span 80 system. The mean vesicle size of niosomes formed from captopril proniosome formulations is given in Table 2. The vesicle size of AGD5 was found to be the least, 1.68 μm ± 0.51. Increasing hydrophobicity of the surfactant monomer led to smaller vesicles, as surface free energy decreases with increasing hydrophobicity.[13] Results of measurement of angle of repose of proniosome powder formulations are summarized in Table 3, which shows that the angle of repose of proniosome power is smaller than that of pure sorbitol. This result was consistent with the angle of repose

Table 3. Angle of Repose of Sorbitol and Formulation

sample no.	formulation code	angle of repose (deg)
1	sorbitol	42.39 ± 0.57
2	AGD4[a]	34.63 ± .062
3	AGD4	36.47 ± 0.43
4	AGD4[b]	38.51 ± 0.24

[a] Mass of sorbitol was half, but the mass of surfactant was kept constant. [b] Mass of sorbitol was doubled, but the mass of surfactant was kept constant.

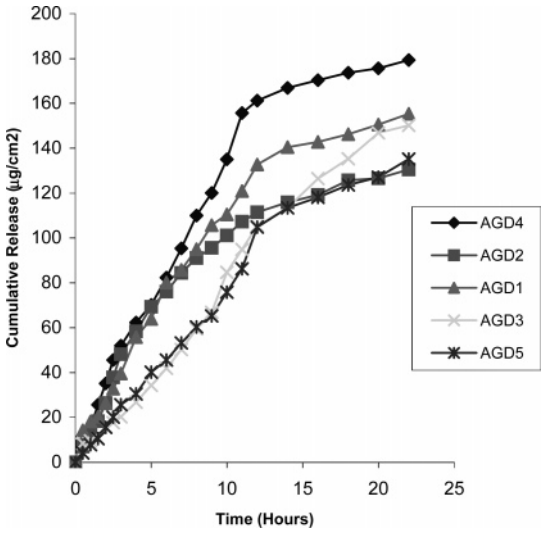

Figure 1. In vitro release profile of proniosomal powder formulation.

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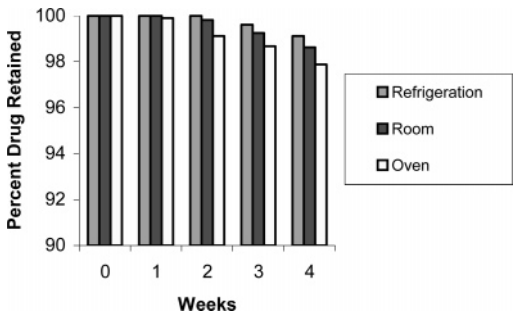

Figure 2. Stability study of formulation AGD4 at different temperatures.

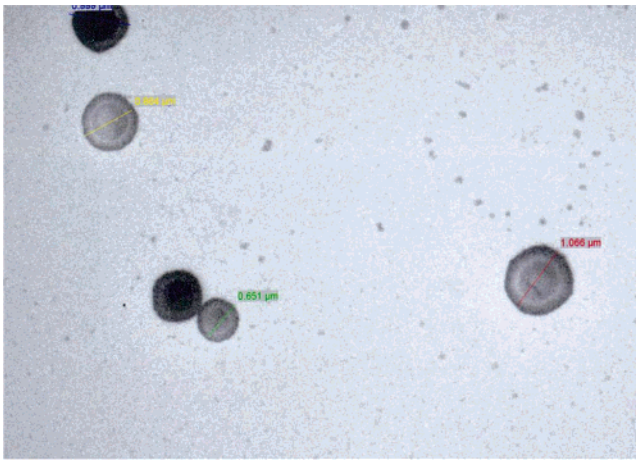

Figure 3. Transmission electron micrograph of AGD2.

of ibuprofen in proniosomes 3. When the proportion of sorbitol to surfactant in the formulation was increased or decreased, the angle of repose of dry proniosome powder was also increased or decreased respectively. Hence the result indicated that proniosomal powder possesses free flow property and can be processed further. TEM (transmission electron microscopy) revealed that niosomes derived from proniosomal power were spherical and homogeneous. The release rate of captopril across dialysis cellophane tubing from AGD4 was best, and it was found to be constant between 11 and 24 h and it follows zero-order kinetics. This may be attributed to the fact that molecules of span 40 and span 60 are in an ordered gel state at an in vitro permeation condition of 25 °C. However, span 80 is in the disordered liquid crystalline state in the same condition.[14] The amount of drug released from different proniosomal powder formulations was found in the order of AGD4 > AGD1 > AGD3 > AGD5 > AGD2.

The amount of drug retained within the vesicles under defined conditions ultimately governs the shelf life of the drug. At all sampling points significantly higher drug retention was observed. Formulations showed more amount of drug retention at refrigeration and room temperature. The shelf life of proniosomal powder formulation is more because, in dry formulations, issues related to hydrolysis of active ingredients or surfactants can be avoided. By forming the suspension as needed, precipitation and aggregation can also be avoided.

Discussion

The objective in developing proniosomes was to devise a method of producing a nonionic surfactant based dosage form at the point of use to avoid the problem of physical and chemical stability found in storage of some surfactant based dosage forms. One of the greatest advances offered by proniosomes is their ease of use. The hydration of proniosome powder is much easier than the long shaking process required to hydrate surfactants in the conventional dry film method. Different formulations using different surfactants, lecithin, and cholesterol were prepared. Span 40 and span 60 were used as representative of nonionic surfactants because it gives vesicles of larger size with higher entrapment of drug.[15] Entrapment efficiency increases with the increase in phase transition temperature of span. Compared to niosomes prepared by conventional means, proniosome-derived niosomes were controlled and may therefore offer improved bioavailability of drug and reduce adverse effects of some drugs. Proniosomes are more convenient and appear to provide improved stability.[16]

Conclusion

In conclusion, we can state that, besides providing the controlled systemic delivery of captopril, proniosome powder provides an effective means of delivering the drug through the oral route, and it can be further processed to make beads, tablets, and capsules, which increase patient compliance. Thus a dry, free flowing product like proniosomes will be a promising industrial product.

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