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Research Article

Formulation and Evaluation of Captopril Loaded Maltodextrin Based Proniosomes

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ABSTRACT

Captopril loaded maltodextrin based proniosome were prepared by slurry method with different surfactant to carrier ratio.The proniosome formulation was evaluated for FT-IR study and Scanning Electron Microscopy.The niosomal dispersion as further evaluated for entrapment efficiency, *invitro* release study, kinetic data analysis, stability study. The result from SEM analysis has smooth surface of proniosome. The formulation F6 which showed higher entrapment efficiency of 97.26% and *invitro* cumulative drug release of 102.26% at the end of 12 hrs. was found to be best among the all 9 formulations. Release was best explained by the First order kinetics. Kinetic analysis showed that the drug release follows Fickian release. Proniosome formulation has showed appropriate stability for 45 days by storing the formulations at different conditions.Captopril provides effective treatment for hypertension and congestive heart failure. However clinical use requires the daily dose of 37.5-75mg to be taken at three times a day. Development of a prolonged action dosage form for captopril will bring many benefits. The development of oral controlled or sustained captopril formulations has been a challenge for a long period of time.

INTRODUCTION

Proniosomes are dry product which could be hydrated immediately before use would avoid many of the problems associated with aqueous niosome dispersions and problems of physical stability (aggregration, fusion, leakage) could be minimized [1]. These dry formulations of surfactant coated carrier can be measured out as needed and rehydrated by brief agitation in hot water [2]. They are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media. Reported methods for preparation of proniosomes were the spraying of surfactant on water soluble carrier particles and the slurry method [2]. This dry free flowing granular product which upon addition of water, disperses or dissolves to form a multilamellar noisome suspension suitable for administration by oral or other routes.

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Captopril (1-[(2S)-3-mercapto-2-methyl propionyl]- 1-proline), an angiotensin converting enzyme, has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered as a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity. It is mainly prescribed for patients who are chronically ill and require long term therapeutic agents. The dose required is 37.5-75mg to be taken three times a day in divided doses. The drug acts orally and after single oral dose ingestion the antihypertensive action is only effective for 6-8hrs [3].The drug is freely water soluble and has elimination half life of 1.7hr. The present study involves formulation of Captopril from maltodextrin based proniosome.

MATERIALS AND METHODS

Captopril obtained as a gift sample from Unicure (India) Pvt. Ltd.,Maltodextrin, Cholesterol, Span 40, Span 60, Brij 72 were purchased from Vertex Pharma, S.D.Fine Chem.Ltd, SPAK Orgochem India Pvt. Ltd, Sigma Aldrich Chemicals.

Preparation of Proniosomes

Proniosomes were prepared by the Slurry Method. Different ratios of formulations were prepared and dissolved in chloroform: methanol (2:1) solution. It was then added to a 100ml round bottom flask containing carrier. Additional chloroform: methanol solution was added to form slurry in the case of lower surfactant loading. The flask was attached to a rotary flask evaporator to evaporate solvent at 60 to 70 rpm a temperature of 45± 2°C and a reduced pressure of 600mmHg until the ,mass in the flask had become a dry free flowing product. These materials were further dried overnight in a dessicator under vaccum at room temperature. This dry preparation was referred to as "Proniosomes" and was used for preparations and for further study on powder properties. These proniosomes were stored in a tightly closed container at refrigerator temperature until further evaluated.

Table 1: Formulation table of Captopril loaded Proniosomes

Formulation Code	Drug (mg)	Maltodextrin (mg)	Cholesterol (mg)	Span 40 (mg)	Span 60(mg)	Brij 72(mg)
FP1	50	40	100	100		
FP2	50	40	100	150		
FP3	50	40	100	200		
FP4	50	40	100		100	
FP5	50	40	100		150	
FP6	50	40	100		200	
FP7	50	40	100			100
FP8	50	40	100			150
FP9	50	40	100			200

Drug Content Analysis

Proniosomal formulation equivalent to 25mg of captopril was taken into a standard volumetric flask. Also vesicles were lysed with 50ml of propane-1-ol and 1ml of the mixture was subsequently diluted with phosphate buffer pH 7.4. The absorbance was measured spectroscopically at 212nm and the drug content calculated [4].

Entrapment Efficiency

Proniosomal preparation was transferred to niosomes by hydrating with phosphate buffer pH 7.4at 80°C using vortex mixer for 2 min. Then the Captopril containing niosomes were separated from unentrapped drug by centrifugation with 14000 rpm at 4°C for 30 min. The supernatant was taken out and diluted with phosphate buffer pH 7.4. The resultant solution was assayed at 212nm sing UV spectrophotometer. The entrapment efficiency of vesicles were found by using following formula [5, 6].

$$\%EE = \frac{CT - CF}{CT} \times 100$$

Where,

C_T = Total drug concentration

C_F = Free drug concentration

Particle Size Analysis

Particle size (z-average diameter), polydispersity index(as a number of the width of the particle size distribution) of Captopril proniosomes was performed by dynamic light scattering also known as photon correlation spectroscopy (PCS) using a Malvern Zetasizer 3000 Nano S (Malvern instruments UK) at 25ºC. Prior to measurements sample was diluted using ultra- purified water to yield a suitable scattering intensity. The diluted niosomal dispersion was poured into the disposable sizing cuvette which is then placed in the cuvette holder of the instrument and analyzed. Air bubbles were removed from the capillary before measurement [7, 8].

Zeta Potential Analysis

Zeta potential analysis (to characterize surface charge of particle) was done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived niosomal dispersion as determined using zeta potential analyzer based on Electrophoretic Light Scattering and Laser Doppler Velocimetry method. The temperature was set at 25°C, charge on vesicles and Mean Zeta potential were obtained [8].

Scanning Electron Microscopy (SEM)

The surface morphology (roundness, smoothness and formation of aggregates) and the size distribution of proniosomes were studied by Scanning Electron Microscopy (HITACHI S 5 GB). A small amount of sample was mounted on a copper stub using double sided adhesive tape and was electrically conductive by coating with a thin layer of gold and SEM images were recorded at 5kV accelerating voltage [9].

***In Vitro* Drug Release Studies**

In- vitro dissolution study of proniosomal powders and pure drug was performed using USP type I (basket) apparatus in continuous medium (pH 7.4) [10]. The medium was maintained at a temperature of 37°C±0.5°C with 50 rpm throughout the experiment. 5ml of samples were collected at predetermined time intervals upto 12 h and replaced with fresh dissolution medium to maintain constant volume. The samples were analyzed by UV spectrophotometer at 212nm [11].

Kinetics of Drug Release

To study the kinetics and mechanism of drug release, the release data of *invitro* dissolution study proniosome were fitted in various kinetic models.

Zero Order Equation

The zero order release kinetics can be obtained by plotting cumulative percentage of drug release Vs Time (h)

$$C = K_0 t$$

Where,

K_0 = zero order constant in conc/time

t = Time in (h)

First Order Equation

A graph was plotted with log percentage cumulative drug remaining Vs time in hours.

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303$$

Where,

C_0 = Initial drug concentration, K = First order constant, t = Time in (h)

Higuchi Kinetics

A graph was plotted with percentage cumulative drug released Vs square root of time.

$$Q = Kt^{1/2}$$

Where,

K = Constant reflecting design variable system (differential rate constant)

t = Time in (h)

The release rate of drug is inversely proportional to the square root of time and is related to the rate of drug diffusion.

Hixson and Crowell Erosion Equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using Hixson and Crowell erosion equation. The graph was plotted by cube root of percentage drug remaining Vs time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} X\ t$$

Where,

Q_0 = amount of drug release at time t

Q_t = initial amount of drug

K_{HC} = rate constant for Hixson Crowell

Korsmeyer –Peppas Equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative percentage drug release Vs log time.

$$M_t / M_a = KT^n$$

M_t / M_a = fraction of drug released at time t

K = Release rate constant

T = Release time

n = Diffusional exponent indicative of the mechanism of drug release.

Stability Studies [12, 4]

The optimized Proniosomes were kept at room temperature as well as at 4°C. Upon 45 days of storage, the physical appearance was done also the drug content and entrapment efficiency were determined.

RESULTS AND DISCUSSION

Proniosomes of Captopril were prepared by slurry method. In this method drug, non-ionic surfactant and cholesterol were mixed in organic solvent and added to maltodextrin carrier. The use of maltodextrin as the carrier in the proniosome preparation permitted flexibility in the amounts of surfactants and other components which greatly enhances the potential application of proniosomes in a scaled up production environment.

The drug content and entrapment efficiency were studied for all the nine formulations represented in Table 2 and 3. The entrapment efficiency was found to be highest with the formulation F6 (97.26%) which may have an optimum surfactant, maltodextrin ratio to provide a high entrapment of Captopril.

Table 2: Drug content of Captopril loaded Proniosomes

Formulation code	Drug content
FP1	83.88%
FP2	89.53%
FP3	**93.95%**
FP4	90.28%
FP5	92.44%
FP6	**97.13%**
FP7	80.63%
FP8	82.23%
FP9	**85.64%**

Table 3: Entrapment efficiency of Captopril loaded Proniosomes

Formulation code	Entrapment efficiency
FP1	80.5%
FP2	83.59%
FP3	**96.51%**
FP4	87.92%
FP5	90.9%
FP6	**97.26%**
FP7	91.6%
FP8	85.61%
FP9	**92.32%**

Table 4: *In vitro* drug release for all formulations (FP1 to FP9)

TIME (Hr)	CUMULATIVE PERCENTAGE DRUG RELEASE (%)									
	Control	**FP1**	**FP2**	**FP3**	**FP4**	**FP5**	**FP6**	**FP7**	**FP8**	**FP9**
0.5	48.93	33.91	32.61	35.58	20.95	18.21	31.25	31.85	38.21	34.81
1	60.14	40.32	36.29	40.29	42.29	22.71	37.80	38.53	44.90	36.92
1.5	85.73	45.69	39.36	41.12	47.62	31.45	44.32	46.21	51.25	39.12
2	92.89	48.38	49.85	44.91	60.81	39.16	47.26	53.29	55.83	43.26
3	101.50	68.18	61.92	48.50	83.69	50.84	50.81	69.21	60.17	51.83
4		77.45	67.24	53.42	98.45	64.91	64.90	81.45	65.91	58.61
5		86.91	73.81	68.70		76.40	75.97	95.60	77.54	66.10
6		102.82	80.12	79.17		84.31	78.29	102.45	82.25	72.86
7			88.14	85.10		93.11	83.11		93.41	79.14
8			95.42	89.29		100.20	88.20		101.70	85.13
9			103.60	94.12			92.96			9.42
10							94.51			100.86
11							95.89			
12							**102.26**			

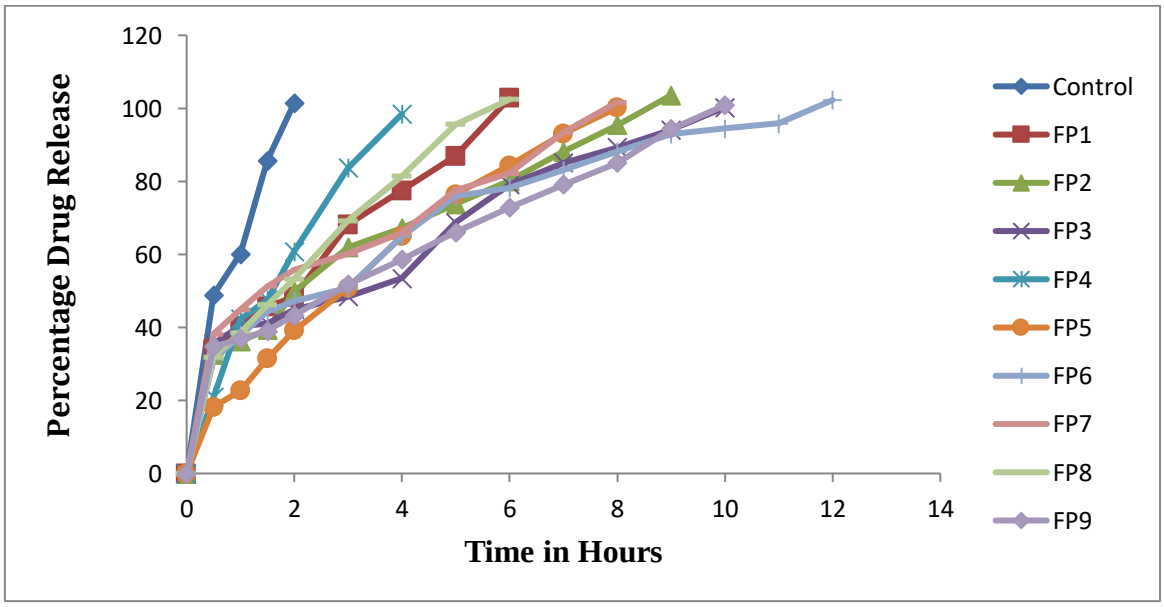

Figure 1: *In vitro* drug release study of Proniosomes (FP1 to FP9)

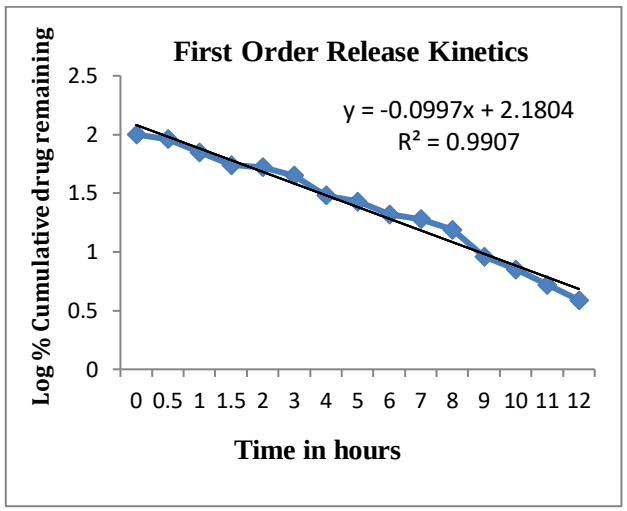

Figure 2: First order release kinetics of optimized FP6 formulation

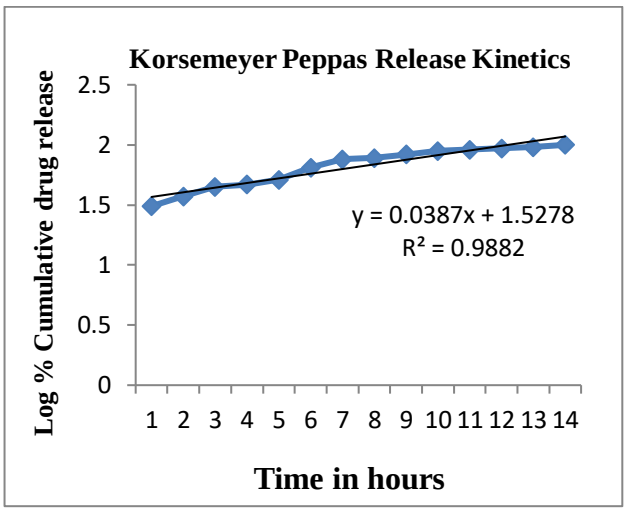

Figure 3: Kinetic model of optimized formulation FP6

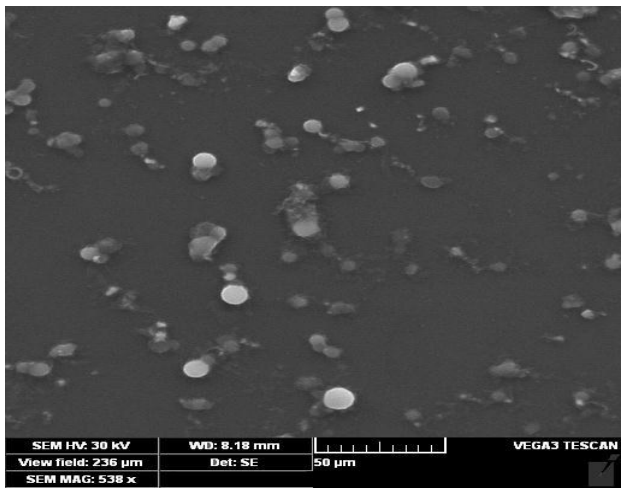

Figure 4: SEM image of optimized formulation FP6

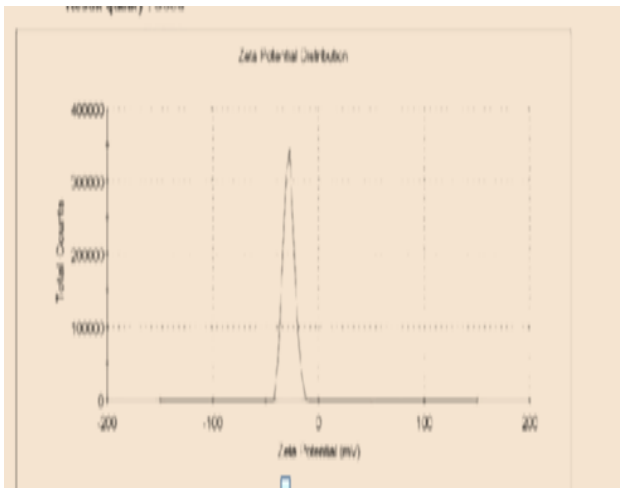

Figure 5: Zeta potential of optimized formulation FP6

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	70.7 nm	3.8 nm	69.9 nm
Total	1.00	70.7 nm	3.8 nm	69.9 nm

Cumulant Operations

Z-Average : 432.1nm
PI : 0.231

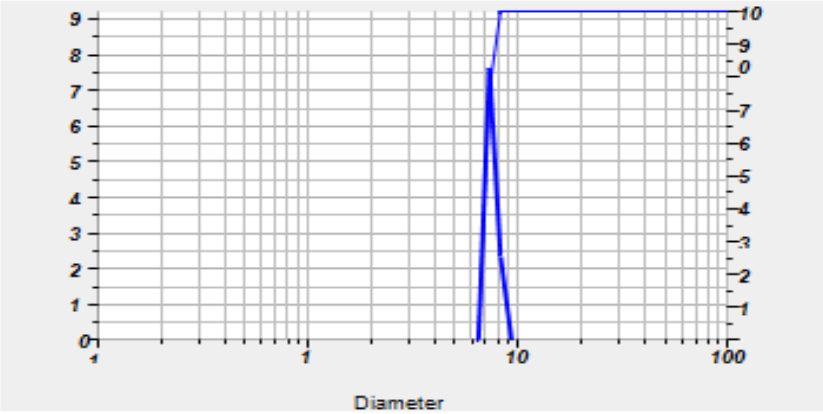

Figure 6: Particle Size of optimized formulation FP6

Table 5: R^2 value of Captopril loaded proniosomes in various kinetic models

Formulation	Zero order	First order	Higuchi	Hixon Crowell's	Korsmeyer and peppas
FP6	0.8839	0.9907	0.9806	0.9868	0.9882

Table 6: Stability Study of Captopril Proniosomes – Optimized Formulation FP6

Time of Storage in Days	Temperature of Storage			
	4°C± 2°C (Refrigerator temperature)		25°C ±2°C (Room temperature)	
	% Drug Content	% Entrapement Efficiency	% Drug Content	% Entrapement Efficiency
0	97.13	97.26	97.13	97.26
15	97.09	97.20	97.11	97.18
30	97.03	97.16	97.08	97.14
45	96.98	97.10	96.97	97.06

Stability studies of the optimized formulation FP6 were carried out by storing at 4°C±2°C (refrigeration temperature) and 25°C± 2°C for a period of 45 days.

The release study was conducted for all the nine formulations as shown in the figure 1, 2 and 3. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 102.26% release within a period of 12 hours. The formulation which have optimum F6 was found to sustain the drug release than other formulations. Among all formulations F6 was selected as best formulation because of its highest entrapment efficiency and consistent release profile of Captopril.

The first order plots showed the First order release characteristics of the formulation, which was confirmed by the correlation value which was found to be nearer to one. Correlation value of Higuchi's plot revealed that the mechanism of drug release was diffusion. The *invitro* kinetic data subjected to log time Vs log drug release transformation plot (Peppa's model), the value lies were found to be n> 0.3 this revealed that the drug release follows a Fickian diffusion.

Shape and surface characteristics of proniosomes were examined by Scanning Electronic Microscopy analysis. Surface morphology showed the smooth surface of optimized proniosomal formulation.

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CONCLUSION

On conclusion, this novel drug delivery system i.e. proniosomes as compared to liposome or noisome represent a significant improvement by eliminating physical stability problems such as aggregration or fusion of vesicles and leaking of entrapped drug during long-term storage. Proniosomes derived niosomes are superior in their conventional of storage, transport and dosing as compare to niosomes prepared by conventional method. By these facts study concluded by Captopril was successfully entrapped within the lipid bilayer of the vesicles with high efficiency and said that proniosomes formed from Span 40, Span 60, cholesterol using maltodextrin as a carrier was a promising approach to sustain the drug release for an extended period of time.

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