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AUGMENTATION OF DISSOLUTION PROFILE OF POORLY SOLUBLE OLMESARTAN MEDOXIMIL FORMULATING INTO PRONISOMES

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ABSTRACT
The present study was designed to investigate the possibility of manufacturing proniosomes and using proniosome-based niosomes as drug carriers. The results reported here indicate that Proniosomes are very promising as drug carriers. The present formulation study on Olmesartan medoximil is an attempt to prepare proniosome based niosomal drug delivery system by slurry method using spray dried lactose as carrier and to evaluate its performance. The proniosomes with various types and contents of nonionic surfactant and cholesterol is evaluated in this study. The proniosome formulation was evaluated for FT-IR study, angle of repose and scanning electron microscopy. The niosomal suspensions were further evaluated for entrapment efficiency, In-vitro release study, Kinetic data analysis, Stability study. The result from SEM analyses has showed porous surface of proniosome. The formulation F9 which showed higher entrapment efficiency of 85.23 ± 1.34 and in-vitro releases of 97.63 ± 0.24% at the end of 13 hr was found to be best among the all 12 formulation. Release was best explained by the first order kinetics. Correlation value of Higuchi's plot revealed that the mechanism of drug release was diffusion. The in vitro kinetic data subjected to log time vs log drug release transformation plot (peppa's model), the value lies were found to be n<0.5 this revealed that the drug release follows a fickian diffusion. Proniosome formulation has showed appropriate stability for 90 days by storing the formulation at accelerated stability condition.

KEYWORDS: Olmesartan medoximil, proniosomal powder, spray dried lactose.

INTRODUCTION
Olmesartan medoxomil is an angiotensin type 2 receptor blocker anti-hypertensive agent, used in the treatment of mild to moderate hypertension. It is a poorly water soluble drug, weakly basic and has oral bioavailability of about 26%. However; its use has been associated with a number of undesirable side effect nausea, vomiting, bloating and abdominal discomfort. These side effects can be avoided by topical administration of the drug.[1,2] Administration of Olmesartan medoximil via the skin could have benefits over oral administration, since it is a non-invasive administration (convenient and safe) and is suitable to people who can't use the oral route due to vomiting or unconsciousness. Moreover, it can reduce the frequency of administration and improve patient compliance.[3]

Proniosome 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 (aggregation, fusion, leaking) could be minimized. These dry formulations of surfactant coated carrier can be measured out as needed and rehydrated by brief agitation in hot water.[4,5] They are water-soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media. Reported methods for preparation of proniosomes are the spraying of surfactant on water-soluble carrier particles and the slurry method.[6] This dry, free-flowing, granular product which, upon addition of water, disperses or dissolves to form a multilamellar niosome suspension suitable for administration by oral or other routes.

Proniosomes are dry formulations of surfactant-coated carrier, which minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing.[7]

The aim of this study was to develop Olmesartan medoximil proniosomal carrier systems using the common, non-irritant, safe and available non-ionic surfactants "Span 20, Span 40, Span 60 and Span 80" with cholesterol. The prepared systems hypothesized to

have controlled release for Olmesartan medoximil over extended period of time.

MATERIALS AND METHODS

Olmesartan Medoxomil was a gift sample obtained from optimus generics Ltd (Hyderabad). spray dried lactose, span20,40,60,80 and cholesterol acetone and isopropyl alcohol were obtained from SD fine chemicals Ltd., Mumbai.

Method of preparation

Proniosomal powders were prepared by using slurry method. The composition of different proniosomal formulations is represented In brief, accurately weighed amounts of lipid mixture comprising of span 60 and cholesterol as per formulation ratios were dissolved in 20ml of solvent mixture containing acetone and isopropyl alcohol (1:1). The resultant solvent solution was transferred into a 250ml round bottom flask and required amount of spray dried lactose was added to form slurry.[8] The flask was attached to a rotary flash evaporator (Hei-VAP/561-01300, Heidolph, Germany) and the organic solvent was evaporated under reduced pressure at a temperature of 45 ± 2^0C. After ensuring the complete removal of solvent, the resultant powders were further dried overnight in a vacuum oven at room temperature so as to obtain dry, free- flowing product. The obtained proniosomal powders were stored in a tightly closed container at 4^0C for further evaluation.

Table 1: C**omposition of various proniosomal formulations.**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	40	40	40	40	40	40	40	40	40	40	40	40
Spray dried lactose (mg)	150	150	150	150	150	150	150	150	150	150	150	150
Span 20 (mg)	20	20	20	-	-	-	-	-	-	-	-	-
Span 40 (mg)	-	-	-	20	20	20	-	-	-	-	-	-
Span 60 (mg)	-	-	-	-	-	-	20	20	20	-	-	-
Span 80 (mg)	-	-	-	-	-	-	-	-	-	20	20	20
Cholesterol	20	60	100	20	60	100	20	60	100	20	60	100
Acetone	10	10	10	10	10	10	10	10	10	10	10	10
Isopropyl alcohol	10	10	10	10	10	10	10	10	10	10	10	10

Micromeritic properties[9]

The flow properties of proniosomal powder were measured by determining the Angle of repose, Carr's index, Hausner's ratio.

Angle of repose

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by allowing the powders to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height (about 2 cm).

$$\theta=\tan^{-1}(h/r)$$

Where
θ= angle of repose
h= height of the heap
r=radius of the base of the heap

Bulk Density

It refers to a measurement to describe packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in mg/ml. It is expressed in g/ml and is given by.

$$\mathbf{P_i=m/v_i}$$

Where,
m = mass of the blend
v_i = untapped volume

Tapped Density

After determining the poured bulk density, Weighed quantity of API was taken into a graduated cylinder. Volume occupied by drug was noted down. Then the cylinder was subjected to 500, 750 & 1250 taps in tap density tester. According to USP, the blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$\mathbf{P_t = m/v_t}$$

Tapped bulk density=Mass of powder/Tapped volume of the powder.

Compressibility Index

Weighed API was transferred to 100ml-graduated cylinder and subjected to 500,750 & 1250 taps in tap density tester. The difference between two taps should be less than 2%. The % of compressibility index calculated using formula.

$$\mathbf{CI = v_i - v_t / v_i * 100}$$

Hausner's Ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

$$\mathbf{Hausner's\ ratio = v_i / v_t}$$

Where v_t = Tapped volume
v_i = untapped volume

Evaluation of proniosomes

Entrapment efficiency

To evaluate the loading capacity of proniosomal systems for olmesartan medoximil, proniosomal powder (100mg) was dispersed in distilled water and warmed a little for the formation of niosomes.[10] Then the dispersion was centrifuged at 18000 rpm for 40min at 5ºC (Remi CPR-24 centrifuge). The clear fraction was used for the determination of free drug at 257.0 nm spectrophotometrically.

The percentage encapsulation efficiency was calculated from Equation.

Percentage Entrapment = Total drug –Diffused drug/total drug×100.

Scanning electron microscopy (SEM)

The surface characteristics of the pure drug spray dried lactose and proniosomal powder was investigated by scanning electron microscope (PW 1729, Philips, Netherlands). Samples were fixed on a brasstub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 10 Kev accelerating voltage.[11]

Fourier transform infrared (FTIR) Specroscopy

Infrared spectra of pure drug, spray dried lactose, non –ionic surfactant and optimized proniosomal powder formulation were obtained using FTIR Specrophotometer by the conventional KBr pellet method.[12]

In-vitro release Study

900ml 0f P^H 6.8 Buffer was placed in vessel and the USP apparatus –II (Paddle Method) was assembled.[13] The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and was operated for 13 hours at 50 rpm. At definite time intervals 5 ml of the fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 257nm using UV-spectrophotometer.

In-vitro release kinetics

To analyze the in-vitro release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is in-dependent of its concentration.[14] The first order describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

Stability studies

The percent entrapment efficiency was assessed by keeping the proniosomal powder at accelerated stability condition, i.e., 40℃ ± 2℃ and 75% RH ± 5% RH.[15] Throughout the study, proniosomal formulations were stored in aluminium foil-sealed glass vials. The samples were withdrawn at different time intervals over a period of one month interval up to three months and % entrapment efficiency from the formulations was analyzed spectrophotometrically.

RESULTS AND DISCUSSION

Micrometric properties of olmesartan medoxomil proniosomes

The powder blends of solid dispersions were evaluated for their flow properties, the results were shown (table.3). angle of repose was in the range from 25 to 34 which indicates good flow of the powder for all formulations. The values of bulk density were found to be in the range from o.472 to 0.510gm/cm3 the tapped density was in the range of 0.493 to o.703 gm/cm3.the values indicate that micrometric properties of the solid dispersions are within the limits and they exhibit good flow properties.

Table 2: Micrometric properties of olmesartan medoxomil proniosomes.

Formulation code	Bulk density	Tapped density	Cars index	Angle of repose	Hausner's ratio
F1	0.445±0.002	0.604±0.001	33.3±0.152	40.23±0.602	0.862±0.001
F2	0.485±0.011	0.493±0.002	25.0±0.57	39.13±1.65	0.752±0.001
F3	0.510.±0.004	0.603±0.001	24.2±0.18	38.46±0.48	0.894±0.002
F4	0.489±0.082	0.628±0.001	27.2±0.13	35.3±1.83	0.809±0.0001
F5	0.496±0.01	0.599±0.002	23.4±0.201	33.3±.74	0.714±0.000
F6	0.482±0.020	0.903±0.001	25.5±0.21	30.13±0.86	0.80±0.001
F7	0.495±0.013	0.509±0.002	15.8±0.416	27.97±1.52	0.815±0.001
F8	0.435±0.15	0.510±0.003	14.0±0.60	26.63±1.25	0.792±0.003
F9	0.474±0.001	0.610±0.021	11.1±0.12	24.93±0.69	0.867±0.001
F10	0.492±0.0.03	0.523±0.023	24.2±0.18	30.4±0.81	0.752±0.001
F11	0.473±0.006	0.641±0.001	31.2±0.063	31.4±1.41	0.800±0.000
F12	0.489±0.032	0.506±0.002	28.2±0.26	32.26±1.25	.800±0.001

Mean ± SD (n=3).

Micromeritic properties

Results indicate small angle of repose assuring good flow properties for proniosome powder formulations. In addition to angle of repose, Carr's index and Hausner's ratio were also less ensuring acceptable flow for proniosome powder formulations.

Entrapment efficiency

The entrapment efficiency ranges from 58% to 85%. The highest entrapment efficiency was exhibited by F9 formulations. Higher surfactant concentration shows the higher entrapment efficiency which might be due to the high fluidity of the vesicles. Results indicate that entrapment efficiency was increased, with increasing cholesterol content and by the usage of span-60 which has higher phase transition temperature.

Table 3: Entrapment efficiency of Olmesartan Medoxomil proniosomes.

Formulation code	Entrapment efficiency (%)
F1	58
F2	57
F3	62
F4	73
F5	77
F6	76
F7	82
F8	83
F9	85
F10	74
F11	75
F12	70

Scanning electron microscopy

Scanning electron microscopy shows the porous surface of the pure spray dried lactose particles, this makes them effective carrier and provides more surface area for the coating of the surfactant mixture. It was confirmed that the optimized formulation had a smooth surface.

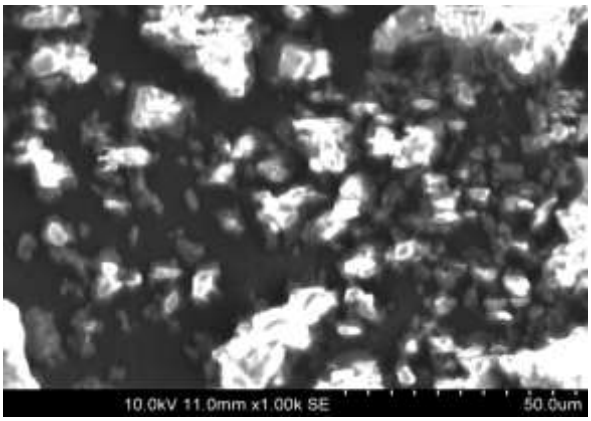


Figure 1: SEM photographs of Optimized formulation.

Fourier transform infrared spectroscopic studies (FTIR)

Chemical interaction between the drug and excipients was studied by using FTIR shown in Figure11. In the FT-IR study all characteristic peaks due to pure were appeared in Cholesterol spray dried lactose based proniosome spectra, which shows no any remarkable change in their position after successful method of preparation. This revealed that there is no chemical interaction and stability of drug during whole method of preparation.

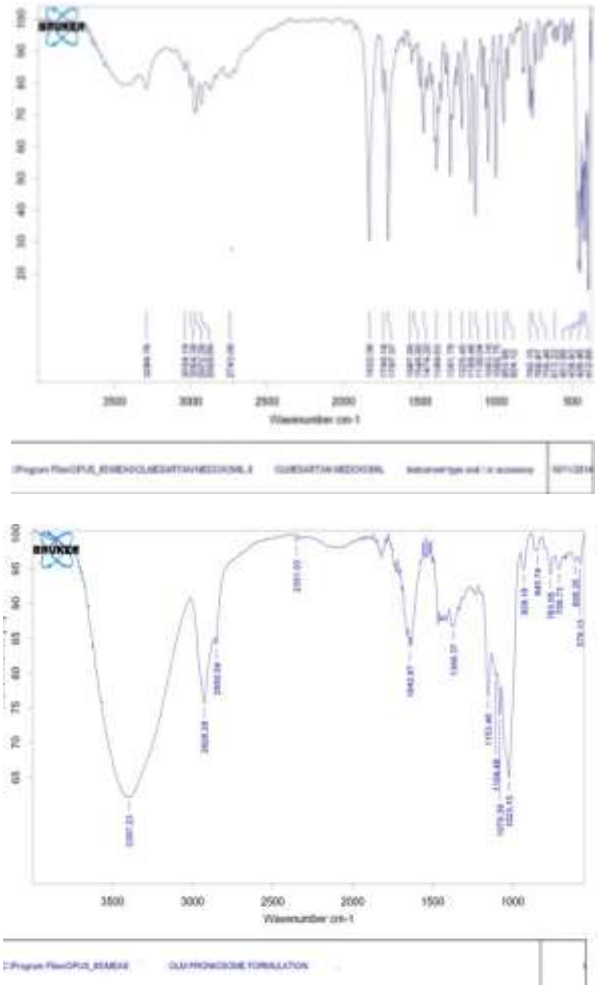
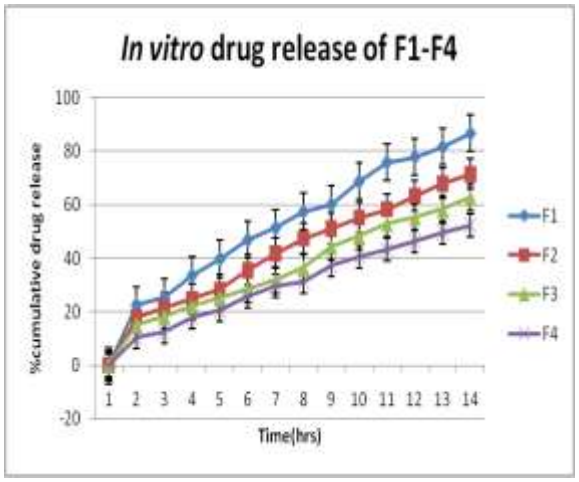
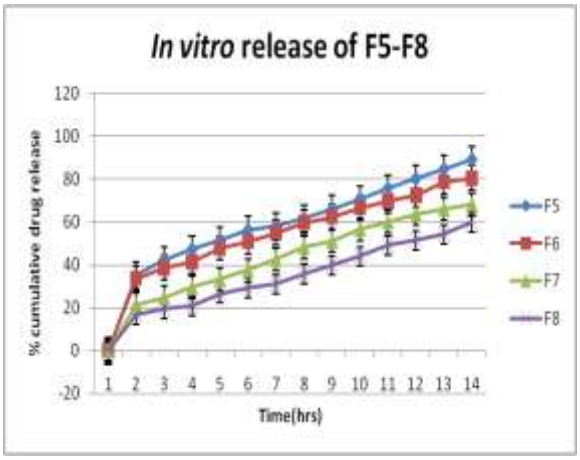


Figure 2: Comparative FTIR spectra of a) olmesartan medoxomil b) formulation of medoxomil In-vitro release Study.

The release study was conducted for all the twelve formulations. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 60% release within a period of 13 hours. The results indicate that optimized olmesartan medoxomil proniosomal formulation showed 97.03±5.64 drug release in 13 hours. The slower release of drug from multilamellar vesicles may be attributed to the fact that multilamellar vesicles consist of several concentric sphere of bilayer separated by aqueous compartment.





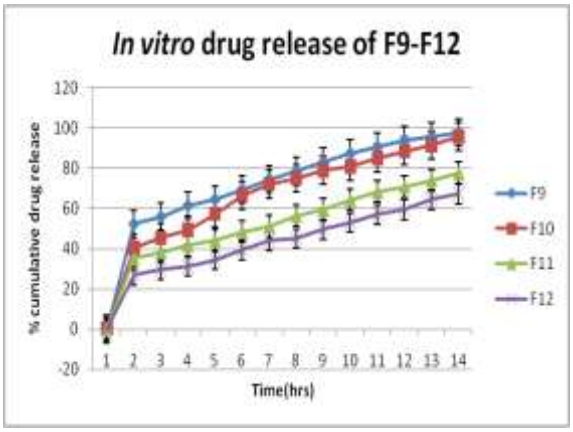


Figure 3: In-vitro dissolution study of olmesartan medoxomil proniosomal formulations.

Release kinetics

The in-vitro release data was applied to various kinetic models. Therefore, it was ascertained that the drug release from all the formulation followed or first order kinetics and Higuchi's plot. Korsmeyer-Peppas plot slope values ranges from 0.462 to 0.499 (lessthan 0.5) which revealed the fact that the drug release follows fickian diffusion.

Table 4: release kinetics of all formulations.

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				R^2 value	'n' value
F1	0.975	0.983	0.949	0.923	0.496
F2	0.945	0.953	0.963	0.857	0.462
F3	0.973	0.951	0.925	0.862	0.464
F4	0.986	0.978	0.966	0.898	0.484
F5	0.979	0.899	0.997	0.964	0.498
F6	0.994	0.911	0.982	0.926	0.499
F7	0.996	0.959	0.967	0.895	0.482
F8	0.984	0.941	0.950	0.873	0.470
F9	0.983	0.994	0.959	0.963	0.490
F10	0.981	0.963	0.970	0.912	0.491
F11	0.993	0.863	0.961	0.888	0.478
F12	0.984	0.886	0.948	0.869	0.468

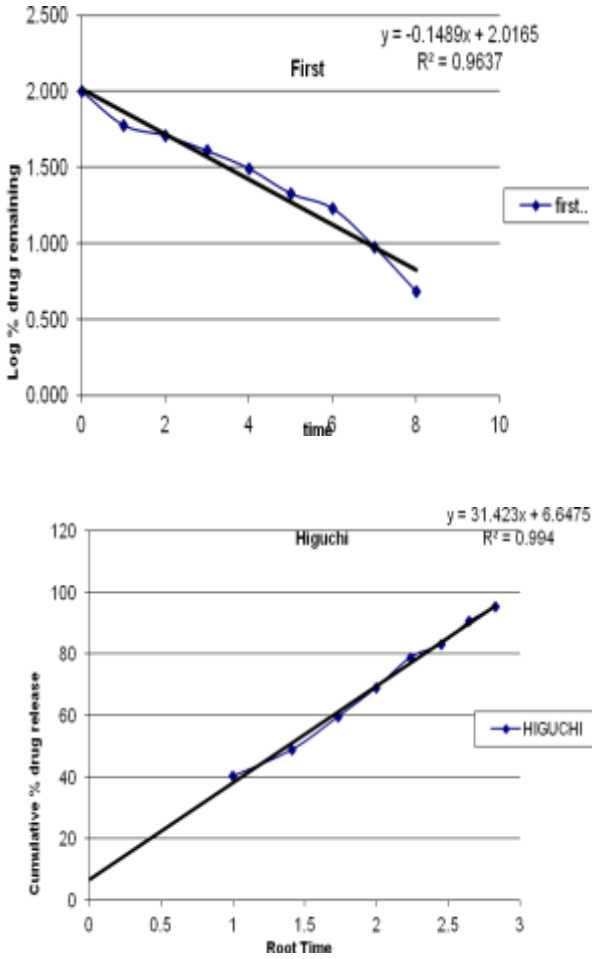


Figure 4: First order and Higuchi kinetics of Optimized Formulation F9.

Stability Studies

On the basis of entrapment efficiency and controlled release property, formulation F9 was selected for the stability studies. Results showed that proniosomal powder formulation was quite stable at accelerated stability condition. Percent drug retained at 40ºC might have decreased due to the melting of surfactant and lipid present in the formulation.

The results of accelerated stability testing were listed in Table. 17 and it show that there was no major effect of temperature and relative humidity ($40^{o}C \pm 2^{o}C$ with 75% RH±5%) on % entrapment efficiency.

Table 5: Stability studies data of Optimized formulation (F9) at Accelerated Stability condition ($40^{o}C \pm 2^{o}C$ with 75% RH±5%).

S. No.	Months	% Entrapment efficiency
1.	0	85 %
2.	1	84.76
3.	2	83.69
4.	3	83.10

CONCLUSION

Olmesartan medoximil is an antihypertensive agent, which belongs to the class of medications called angiotensin II receptor blockers. Proniosomes are very promising as drug carriers which eliminate physical stability problems such as aggregation or fusion of vesicles and leaking of entrapped drugs during long-term storage. Results indicate that entrapment efficiency was increased, with increasing cholesterol content and by the usage of span-60 which has higher phase transition temperature. In-vitro release studies indicate that optimized olmesartan medoxomil proniosomal formulation showed 97.03±5.64 drug release in 13 hours. The in vitro release data was applied to various kinetic models and which revealed the fact that the drug release follows fickian diffusion.Scanning electron microscopy shows the porous surface of the pure spray dried lactose particles, this makes them effective carrier and provides more surface area for the coating of the surfactant mixture. By these facts of study it can be concluded that proniosomes formed from span 60 and cholesterol in the ratio 20:100 (in mg) where 150 mg of carrier used is a promising approach to control the drug release.

Based on the above data, it was confirmed that prepared Olmesartan medoximil proniosomes formulation F9 can be considered as useful approach to treat Hypertension.

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