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Formulation and Evaluation of Pronisomal Based Drug Delivery System of Flurbiprofen

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Abstract: The present study on Flurbiprofen is an attempt to prepare proniosome based drug delivery system by slurry method using various non-ionic surfactants, namely span 20 (Sp 20), span 40 (Sp 40), span 60 (Sp 60) and span 80 (Sp 80) with cholesterol and spray dried lactose as carrier and to evaluate its performance. The proniosome formulation was evaluated for angle of repose, scanning electron microscopy, entrapment efficiency, In-vitro release study, Kinetic data analysis, Stability study. The result from SEM analysis has showed porous surface of proniosome. The formulation F9 which showed higher entrapment efficiency of 86.23 ± 1.34 and *in-vitro* release of 96.63 ± 0.24% at the end of 13 hrs was found to be best among the all twelve formulations. Release was best explained by the first order kinetics. The n value was found to be n<0.5, this revealed that the drug release follows fickian diffusion. Proniosome formulation has showed appropriate stability for 90 days by storing the formulation at accelerated stability condition.

Key words: Flurbiprofen, proniosomal powder, spray dried lactose, Span 20, 40, 60

Introduction:

Basic object of drug therapy is to provide therapeutic amount drug to proper site in body to promptly achieve and then maintain desired drug concentration in order to produce desired effect. Recently in the field of pharmaceutical sciences enormous efforts are being aimed at the refabrication of existing drugs and drug delivery system in order to solve the problem related to poor solubility, poor bioavailability, dosing problem, stability, toxicity etc. This technique of working has lead to development of new drug and new drug delivery system in a more perfect form. [1]

Non-ionic surfactant vesicles known as niosomes are gaining attention as an alternative prospective drug delivery system to conventional liposomes. Niosomes have revealed advantages as drug carriers such as being cheap and chemically stable alternative to liposomes, but they are allied with problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage.[2] The proniosome approach minimizes these problems by using dry, free flowing product, which is more stable during sterilization and storage.

Provesicular systems had attracted researchers as an alternate strategy for transdermal delivery of drugs because of the non-toxicity and penetration effect of lecithin/surfactants. Provesicular systems have been exploited in oral drug delivery in the form of tablets, beads or capsules and have shown improved dissolution and absorption characteristics. Based on the investigations provesicular systems appear to be an alternate drug carrier for various routes of drug administration.

Flurbiprofen is a derivative of phenylalkanoic acid, a nonsteroidal anti-inflammatory drug (NSAID) related to ibuprofen in structure. The commercial dosage forms of flurbiprofen are tablets, sustained release capsules, and eye drops. It is used in the treatment of gout, rheumatoid arthritis, osteoarthritis and other rheumatic disorders. Administration of flurbiprofen 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. [3]The transdermal route also can avoid gastrointestinal (GI) incompatibility, first pass metabolism and the GI side effects of the drug. Moreover, it can reduce the frequency of administration and improve patient compliance. Flurbiprofen was formulated as proniosomes to overcome the problem like gastric side effect, short half life and low bioavailability.

The aim of this study was to develop flurbiprofen proniosomal carrier systems using the common, non-irritant, safe and available non-ionic surfactants "Sp 20, Sp 40, Sp 60, and Sp 80" with cholesterol. The prepared systems hypothesized to have controlled release for flurbiprofen over extended period of time. To investigate the possibility of using proniosomal systems for transdermal delivery of drugs, *in vitro* release and permeation studies of flurbiprofen were tested and compared with some other suspension forms of the drug using cellophane membranes and rabbit skin. The effect of cholesterol on drug permeation was also evaluated.

Materials and methods

Flurbiprofen was obtained as a gift sample Aurobindo Pharma 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:

Twelve formulations of proniosmes were prepared by Slurry method.[4] The non-ionic surfactants used are Span (20, 40, 60 and 80). The coating carriers used is spray dried lactose; membrane stabilizers like cholesterol are also used (Table 1).

For ease of preparation a stock solution of accurately weighted quantities of surfactant, cholesterol and drug was prepared in acetone: isopropyl alcohol (2:1) solution. The required volume of surfactant, cholesterol solution and drug was added to a 100 ml round bottom flask containing 200 mg spray dried lactose carrier. Additional acetone: isopropyl alcohol solution was added to form slurry in the case of lower surfactant loading. The flask was attached to a rotary evaporator to evaporate solvent at 60-70 rpm, a temperature of 45±2ºc and a reduced pressure of 600 mm Hg until the mass in the flask had become a dry free flowing product. These materials were further dried overnight in desiccator under vacuum at room temperature. This dry preparation is referred to as Proniosomes Powder.

Measurement of Angle of repose:

The angle of repose of dry proniosomes powder and spray dried lactose powder was measured by a funnel method. The spray dried lactose powder or proniosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. [5]

The powder flows 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.

Characterization of proniosomes

Provesicles were characterized for vesicle size and morphology, entrapment efficiency, *In-vitro* release and permeation studies, stability studies etc

Vesicle size and morphology

Vesicle morphology involves the measurement of size and shape.[6] The size of the vesicles was measured by optical microscopy in two conditions i.e: with agitation and without agitation. Hydration without agitation results in largest vesicle size. Surface morphology means roundness, smoothness and formation of aggregation; studied by scanning electron microscopy.

Determination of Encapsulation Efficiency

Per cent encapsulation efficiency (EE) was determined by centrifugal method.[7] The proniosomal dispersion was centrifuged (18000 rpm) for 40 min at 5˚C in order to separate unentrapped drug. The supernatant was taken and diluted with Phosphate buffer pH 7.4. The drug concentration in the resulting solution was assayed spectrophotometrically at 247 nm. The percentage of drug encapsulation was calculated by the following:

$$\mathbf{EE\ (\%) = [(Ct - Cf)/ Ct] \times 100}$$

Where,

Ct is the concentration of total drug and

Cf is the concentration of unentrapped drug.

***In-vitro* Drug Release of proniosomal powder**

The *in-vitro* drug release studies were carried out by means of treated dialysis membrane. The release rate of Flurbiprofen from proniosomal powder was carried out in using dialysis bag method. [8]

A measured amount of drug equivalent to 10 mg were placed dialysis bag of effective length 8 cm. Dialysis bag was placed in a beaker containing 500 ml of Phosphate buffer pH 7.4. The beaker was placed over magnetic stirrer having stirring speed of 100 rpm. The temperature of medium was maintained at 37ºC by a thermostatic control available on the magnetic stirrer. Aliquots of sample (5 ml) were withdrawn periodically and replaced with the same volume of fresh fluid, at each sampling point. The samples withdrawn were analyzed for the drug content at 247 nm spectrophotometrically. All the determination was made in three times.

Drug Release Kinetic Data Analysis:

The release data obtained from various formulations were studied further for their fitness of data in different kinetic models like Zero order, First order, Higuchi's and Korsemeyer peppa's mechanism.[9,10]

Stability Studies:

After measuring the initial percentage entrapment of the drug in the optimized formulation, the formulation were stored in sealed glass ampoules room temperature 4-8 ˚C and 37˚C for a period of at least 30 days . [11]The percentage entrapment of the drug was determined in the after 30 days to know the amount of drug leaked out. The percent drug lost was calculated taking the initial entrapment of drug as 100%.

Results and Discussion

Angle of Repose:

The angle of repose showed that the proniosome powder had smaller angle of repose (Table 2). This is due to the smooth surface of proniosome powder which is consistent with the scanning electron microscopic observation.

Vesicle size and morphology

The prepared vesicles were studied under 100x magnifications to observe the formation of vesicles. Some unevenness of vesicles that observed under the study may be due to drying process under normal environment condition. The relationship observed between proniosme size and span hydrophobicity has been attributed to the decrease in surface energy with

increasing hydrophobicity, resulting in the smaller vesicles. Increasing the cholesterol content also contributed in increasing the hydrophobicity, with a subsequent slight reduction in vesicle size. The particle size of various formulations varied due to variation in the composition of formulations and the mean particle size in the range of 55.62 ± 0.58µm to 97.49 ± 0.57µm (Table 3).

Shape and surface characteristic of proniosome were examined by Scanning Electronic Microscopy analysis. Scanning electron microscopy shows the porous surface of the pure spray dried lactose particles, this makes them

Table 1: Formulation Chart of Flurbiprofen proniosomes formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Spray dried lactose (mg)	200	200	200	200	200	200	200	200	200	200	200	200
Span 20 (mg)	25	25	25	-	-	-	-	-	-	-	-	-
Span 40 (mg)	-	-	-	25	25	25	-	-	-	-	-	-
Span 60 (mg)	-	-	-	-	-	-	25	25	25	-	-	-
Span 80 (mg)	-	-	-	-	-	-	-	-	-	25	25	25
Cholesterol	25	75	125	25	75	125	25	75	125	25	75	125
Acetone	20	20	20	20	20	20	20	20	20	20	20	20
Isopropyl alcohol	10	10	10	10	10	10	10	10	10	10	10	10

Table 2: Measurement of Angle of Repose

Formulation code	Angle of repose
F1	38.23±0.602
F2	39.13±1.65
F3	38.46±0.48
F4	35.31±1.83
F5	33.30±0.74
F6	30.13±0.86
F7	27.93±0.69
F8	26.63±1.25
F9	24.97±1.52
F10	30.42±0.81
F11	31.40±1.41
F12	32.26±1.25

Mean ± SD (n=3)

Table 3: Particle size of all formulations

Formulation code	Mean particle size (µm)
F1	61.48 ± 0.57
F2	57.35 ± 0.44
F3	55.62 ± 0.58
F4	73.28 ± 0.57
F5	68.35 ± 0.77
F6	61.55 ± 0.44
F7	85.36 ± 0.57
F8	79.20 ± 0.57
F9	76.58 ± 0.54
F10	97.49 ± 0.57
F11	92.36 ± 0.57
F12	89.43 ± 0.44

Mean ± SD (n=3**)**

effective carrier and provides more surface area for the coating of the surfactant mixture (Figure 1).

Entrapment Efficiency:

Drug entrapment within a vesicular carrier is an important parameter to be defined to really to evaluate the loading capacity of proniosomal systems. For this reason, the entrapment efficiency of flurbiprofen within the formulations varies from as low as varies from 55.02 % for Span 20 (F1) to high as 86.57 % for span 60 (F9) Table 4, high entrapment efficiency for span 60

formulation can be attributed to its length of longer side chain, and it easily diffuses into the receptor fluid membrane integrity, orientation and packaging ability.

The proniosomal formulation having low cholesterol content was found to cause low entrapment efficiency, which might be because of leakage of vesicle. It is observed that very high cholesterol content had a lowering effect on drug entrapment to the vesicles. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment.

Table 4: Entrapment Efficiency of all formulations

Formulation code	Entrapment Efficiency (%)
F1	55.02
F2	62.58
F3	58.23
F4	71.46
F5	79.03
F6	77.82
F7	80.16
F8	86.57
F9	83.39
F10	70.86
F11	77.36
F12	72.15

Table 5: Release kinetics of all formulations

Formulation	Zero order (R^2)	First order (R^2)	Higuchi Matrix (R^2)	Hixson-Crowell (R^2)	Korsemeyer-peppas	
					R^2	n-value
F1	0.9672	0.9759	0.9836	0.9900	0.9764	0.4965
F2	0.9758	0.9889	0.9731	0.9916	0.9601	0.4623
F3	0.9757	0.9792	0.9524	0.9822	0.9419	0.4651
F4	0.9871	0.9967	0.9662	0.9759	0.9836	0.4847
F5	0.8792	0.9432	0.9768	0.9530	0.9656	0.3580
F6	0.8794	0.9689	0.9810	0.9561	0.9625	0.3581
F7	0.9531	0.9903	0.9878	0.9846	0.9696	0.4533
F8	0.9689	0.9782	0.9629	0.9795	0.9364	0.4246
F9	0.8297	0.9788	0.9766	0.9795	0.9929	0.3568
F10*	0.8552	0.9604	0.9801	0.9716	0.9700	0.3639
F11	0.8700	0.9628	0.9699	0.9464	0.9322	0.3327
F12	0.9126	0.9660	0.9778	0.9565	0.9346	0.3886

Table 6: % Entrapment efficiency after stability studies

Number of days	% Entrapment Efficiency at temperature 4-8 ˚C	% Entrapment Efficiency at temperature 37˚C
0	100 %	100 %
10	99.60	99.00
15	97.80	96.80
30	95.10	94.70

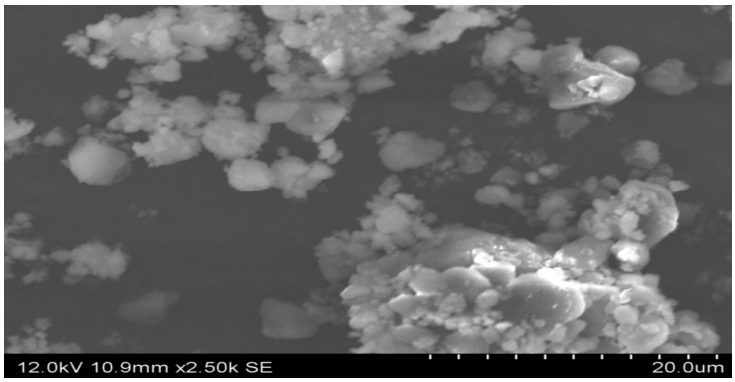

Figure 1: SEM photomicrographs of optimized formulation F9

In-*Vitro* Drug Release Studies:

The release study was conducted for all the twelve formulations in the phosphate buffer pH 7.4. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 90 % release within a period of 13 Hrs.

Cholesterol which has a property to abolish gel to liquid transition of proniosomes, this found to prevent the leakage of drug from the formulation. 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.

This result is in accordance with increasing cholesterol beyond a certain concentration can disrupt the regular linear structure of the vesicular membrane and increase the drug release. The results indicate that optimized flurbiprofen proniosomal formulation showed 96.63±0.2 drug release in 13 hours (Figure 2, 3, 4, 5).

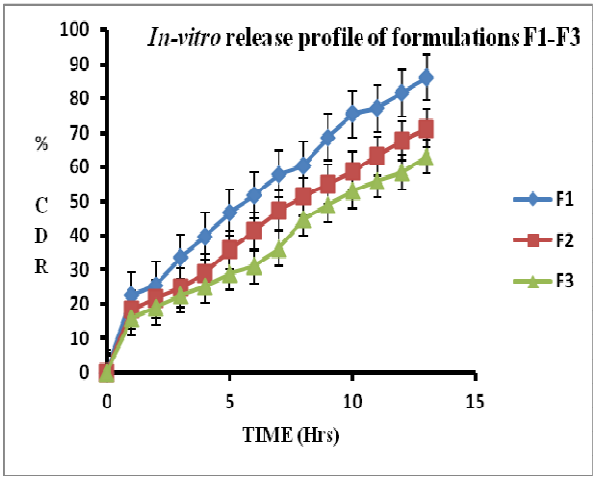

Figure 2: *In-vitro* release profile of F1-F3

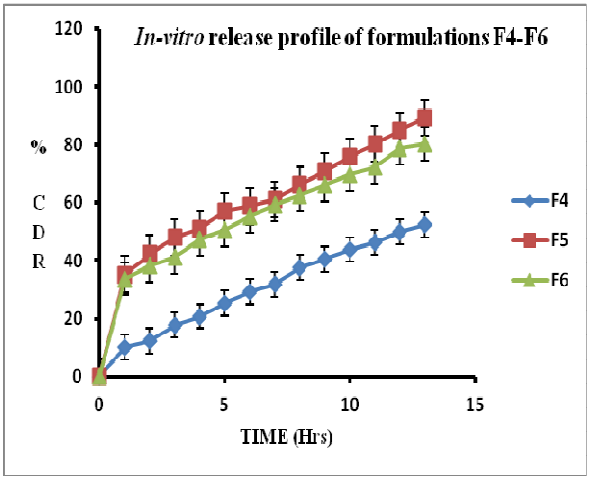

Figure 3 : *In-vitro* release profile of F4-F6

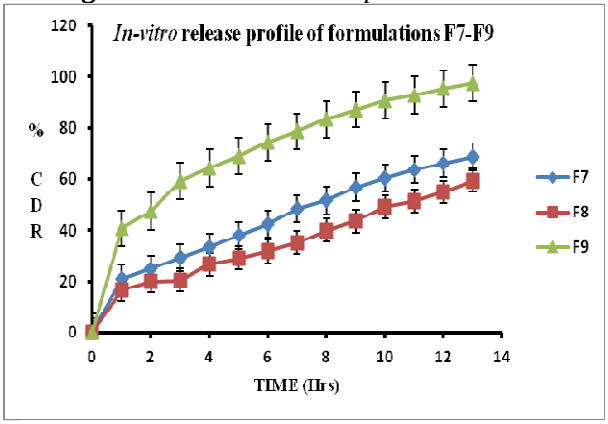

Figure 4 : *In-vitro* release profile of F7-F9

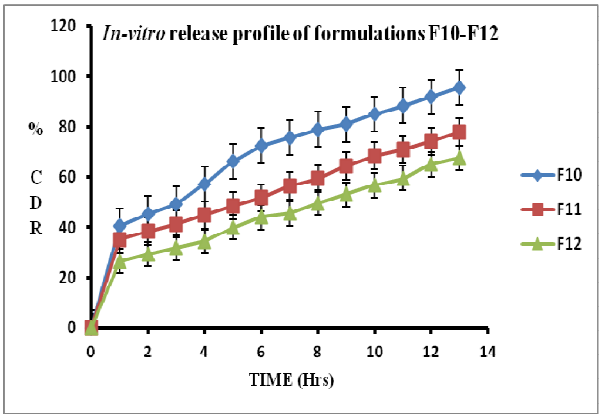

Figure 5 : *In-vitro* release profile of F10-F12

Kinetic Data Treatment

The release data were analyzed mathematically according to zero-order, first order, and Higuchi equations. From the study it was found that formulation F9 exhibited satisfactory results, hence considered as better formulation. In order to ascertain release kinetics,

the rate constant for zero order, first order and Higuchi equation kinetics were calculated for each time interval, the release constant was calculated from the slope of appropriate plots, and the regression coefficient (r^2) was determined. It was found that the *in-vitro* drug release of proniosome was best explained by first order kinetics for best formulation F9 as the plots show highest linearity (Table 5 & Figures 6, 7, 8, 9, 10).

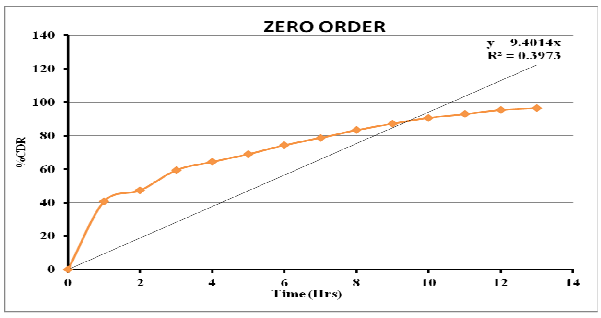

Figure 6: Zero order of F9

Figure 7: First order of F9

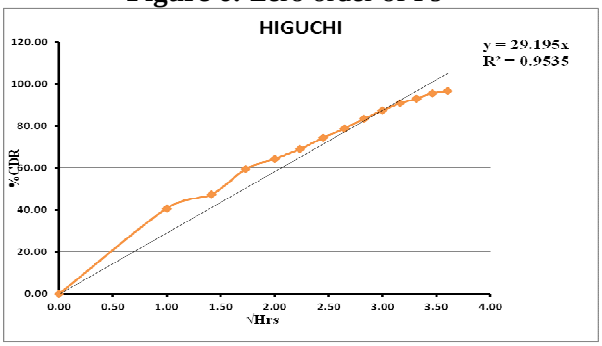

Figure 8: Higuchi release of F9

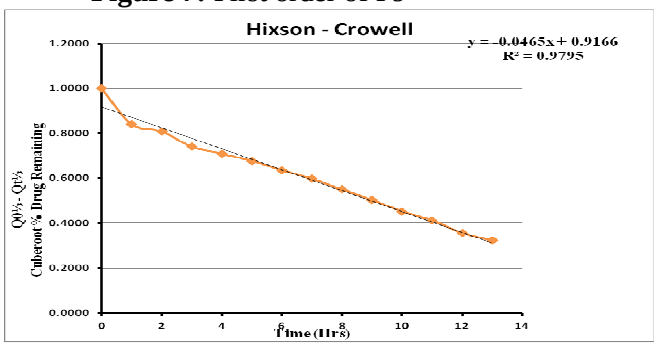

Figure 9: Hixson-crowell release of F9

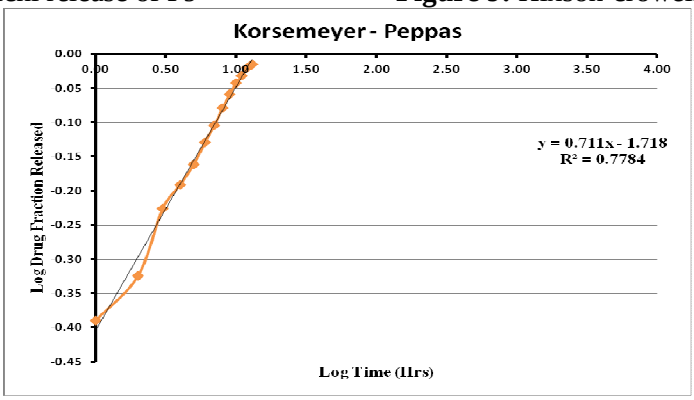

Figure10: korsemeyer-peppas of F9

Physical stability of proniosomal formulations were studied for a period of one month. The EE were determined for all proniosomal formulations stored at 4-8 ˚C and 37˚C as shown in Table 6, which indicates insignificant decrease in EE of proniosomes stored at 4-8 ˚C: approximately 90% of flurbiprofen was retained in all proniosomal formulations after the one-month period. Thus, Span 60 proniosomes of flurbiprofen seemed to exhibit good stability at low temperature.

Conclusion

In this investigation, proniosomal systems of different non-ionic surfactants which are available and cheap are easily prepared. 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.

The proniosomal formulation having low cholesterol content was found to cause low entrapment efficiency and very high cholesterol content had a lowering effect on drug entrapment to the vesicles. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment. In-vitro release studies indicate that optimized flurbiprofen proniosomal formulation showed 96.63±0.2 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 25:125 (in mg) where 200 mg of carrier used is a promising approach to control the drug release.

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