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Development And Evaluation Of Lornoxicam Loaded Maltodextrin Based Proniosomes

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Abstract : Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier "Proniosomes". Proniosomes is a dry formulation using suitable carrier coated with non-ionic surfactants and can be converted into niosomes immediately before use by hydration. These proniosome derived niosomes are as good as or even better than conventional niosomes. Lornoxicam loaded Maltodextrin based proniosomes were prepared by slurry method with different surfactant to cholesterol ratio.The proniosome formulations were 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 confirmed the coating of surfactant on the surface of carrier. The formulation F_3, which showed higher entrapment efficiency of 72.69% and invitro release of 91.17 % at the end of 24h, was found to be best among the all 7 formulation. Release was best explained by the zero order kinetics. Kinetic analysis shows that the drug release follows super case II transport diffusion. Proniosomes formulation has showed appropriate stability for 90 days when compared with reconstituted niosomes by storing the formulation at refrigerator condition.
Keywords: Lornoxicam, Proniosome, Maltodextrin, Span-60, FT-IR, SEM, Zero order, Kinetic analysis.

Introduction

Lornoxicam is a non steroidal anti inflammatory drug mainly used as analgesic.The proniosomal formulation of lornoxicam helps to sustain the analgesic effect [1]. Sustained release dosage form delivers the drug at a slow release rate over an extended period of time to achieve the objective. The short biological half life (about 3-5 hours) and dosing frequency not more than once a day makes lornoxicam an ideal candidate for sustained release [2]. Proniosomes are dry product which could be hydrated immediately before use would avoid many of the problems associated with aqueous noisome 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. 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.This dry free flowing granular product upon addition of water, disperses or dissolves to form a multilamellar niosomal suspension suitable for administration by oral or other routes. Nowadays considerable interest has been focused on niosomes based targeted drug delivery. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs [3].

Materials And Methods

Lornoxicam obtained as a gift sample from Aeon biologicals Chennai (India). Cholesterol obtained from Merck Specialities Pvt. Ltd., Mumbai (India). Maltodextrin and Span 60 obtained from National chemicals, Ahmedabad (India). Chloroform from Suvinadh chemicals, Baroda (India). Rotary flash evaporator for the preparation of niosomes procured from Popular India, Dialysis membrane for the study of *in-vitro* release obtained from Hi media India. All other materials used and received were of analytical grade.

Proniosome preparation

The slurry method was selected for the preparation of proniosomes using maltodextrin as a carrier. For ease of preparation, a 250µmol stock solution of span60 and cholesterol was prepared in chloroform and methanol (2:1) solution. The required volume of span60, cholesterol stock solution and drug dissolved in chloroform and methanol (2:1) solution was added to a 100ml round bottom flask containing the maltodextrin carrier. Additional chloroform and methanol solution added to form slurry in the case of lower surfactant loading. The flask was attached to a rotary flash evaporator to evaporate solvent at 60 to70 rpm, a temperature of 45 ± 2ºC, and a reduced pressure of 600mmHg until the mass in the flask had become a dry, free flowing product [4]. These materials were further dried overnight in a desiccator under vacuum at room temperature. This dry preparation is referred to as 'proniosomes' and was used for preparations and for further study on powder properties. These proniosome were stored in a tightly closed container at refrigerator temperature until further evaluated.

Preparation of niosomes from proniosomes: Proniosomes were transformed to niosomes by hydrating with hot water 80ºc and by gentle mixing. The niosomes were sonicated twice for 30sec using sonicator and then evaluated for further studies. [5]

Evaluation of Proniosomes

Angle of repose

The angle of repose of dry proniosomes powder and maltodextrin powder was measured by a funnel method. The maltodextrin powder or proniosome powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 2cm above a level black surface. 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 [6].

Surface Morphology

Surface morphology was performed by scanning electron microscopy. Small amount of powder samples were placed on a stud and platinum was coated on them by auto sputter fine coater. Then the platinum coated samples were analysed in a cold field emission scanning electron microscope and photographed [6,7].

Microscopy

The vesicle formation by the particular procedure was confirmed by optical microscopy in 400x resolution. The noisome suspension placed over a glass slide and fixed over by drying at room temperature,the dry thin film of noisome suspension observed for the formation of vesicles. The photomicrograph of the preparation also obtained from the microscope by using digital SLR camera [7].

Entrapment efficiency

Niosome entrapped lornoxicam was estimated by dialysis method. The niosomes were placed in the dialysis bag 50 (presoaked for 24 hrs). Free lornoxicam was dialyzed for 30 minutes each time in 100 ml of phosphate buffer saline pH 7.4. The dialysis of free lornoxicam always completed after 12-15 changes, when no lornoxicam was detectable in the recipient solution [8]. The dialyzed Lornoxicam was determined by finding out the concentration of bulk of solution by UV spectrophotometer at 376nm. The samples from the bulk of solution diluted three times before going for absorbance measurement. The free lornoxicam in the bulk of solution gives us the total amount of un-entrapped drug. Encapsulation efficiency is expressed as the percent of drug trapped.

$$\text{Percent Entrapment} = \frac{Total\ drug - diffused\ drug}{total\ drug} \cdot 10_0$$

***Invitro* release Study**

In vitro release pattern of niosomal suspension was carried out in dialysis bag method. 5ml of niosomal suspension was taken in dialysis bag (Hi media) and the bag was placed in a beaker containing 100 ml pH7.4 phosphate buffer . The beaker was placed over magnetic stirrer and the temperature was maintained at 37+10C. 5 ml samples were withdrawn periodically and were replaced by fresh buffer. The sink condition was maintained throughout the experiment [9]. The withdrawn samples were analyzed for drug content using UV spectrophotometer at 376 nm keeping phosphate buffer pH 7.4 as blank.

Drug Release Kinetic Data Analysis.

The release data obtained from various formulations were studied further for their fitness in the zero order release pattern. The study was conducted by checking the fitness of data in models like Higuchi's and peppa's.

Stability Study

Physical stability

Physical stability study was carried out to investigate the leaching of drug from niosome (in a suspension) during storage . The best formulation F3 was kept at refrigerated temperature (2-8^{0}c), room temperature and 40^{0}c (75%RH) as three different groups. Stability chamber was used for the third group. Best three (F3,F4,F5) of the optimized Lornoxicam niosomal suspension composed of span 60 and cholesterol sealed in glass vials and stored in refrigerated temperature(2-8^{0}C) for a period of 3 months [10]. Samples from each batch were withdrawn after the definite time intervals and the residual amount of drug in the vesicles was determined. Stability data of three formulations were further analyzed for significant difference by paired t-test [11].

Zeta potential analysis

Zeta potential was analyzed to measure the stability of niosome by studying its colloidal property. The study was conducted using zeta potential probe (model DT-300)[11]. The formulation F_4 which was found to have a better physical stability was further analyzed by this method for its vesicular stability [12].

Results And Discussion

FT-IR spectra of lornoxicam, maltodextrin, physical mixture of drug and best formulation F_3 were recorded. Lornoxicam present in the formulation F_3 formulation was confirmed by FT-IR Spectra. FT-IR studies indicate no chemical interaction between lornoxicam and carrier as it is shown in the Figure 1, 2 and 3.

Angle of repose of maltodextrin powder compared with proniosome formulation by fixed funnel method. Results of measurement of the angle of repose of proniosome powder and pure maltodextrin are summarized in Table 2. and indicate that the angle of repose of dry proniosome powder is smaller than that of pure maltodextrin.If the proportion of surfactant in the formulation decreases slightly. It indicate that the fluidity of proniosomes dry powder, so further processing of proniosome powder as a beads, tablets or capsules is possible.

Shape and surface characteristics of proniosomes were examined by scanning electron microscopy analysis.Pure maltodextrin and lornoxicam loaded maltodextrin proniosome (F_3 formulation) are evaluated for surface morphology. Scanning electron microscopy shows the porous surface of the pure maltodextrin particles, this makes them effective carrier and provides more surface area for the the coating of the surfactant mixture. Surface morphology illustrates the smooth surface of proniosome formulation as it shown in Figure 4.. The prepared vesicles were studied under 400x 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 particles are found to be uniform in size and shape as clearly visible in the Figure 5. Entrapment efficiency was studied for all the 7 formulations to find the best in terms of entrapment efficiency. Higher entrapment efficiency of the vesicles of span 60 is predictable because of its higher alkyl chain length. The entrapment efficiency was found to be higher in F3 (72.69%), as shown in the Table 1, which may have an optimum cholesterol surfactant ratio to provide a high entrapment of lornoxicam. The proniosomal formulations having high surfactant concentration (F_3, F_4 and F_5) have the higher entrapment efficiency which might be due to the high fluidity of the vesicles. Very low cholesterol content (F_1) was also found to cause low entrapment efficiency (65.37%), which might be because of leakage of the vesicles. It was also observed that very high cholesterol content (F_7) had a lowering effect on drug entrapment to the vesicles (58.26%). 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. The higher entrapment may be explained by high cholesterol content (~50% of the total lipid). There are reports that entrapment efficiency was increased, with increasing cholesterol content and by the usage of span-60 which has higher phase transition temperature. The larger vesicle size may also contribute to the higher entrapment efficiency. Entrapment efficiency showed by various formulations is specified in Table 1. The release study was conducted for all the 7 formulations. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 80% release within a period of 24 hours. Cholesterol, which has a property to abolish the gel to liquid transition of niosomes, this found to prevent the leakage of drug from the niosomal 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. Formulations F_1, F_2, have sustained release. The above specified three best formulations F_3, F_4 and F5 were found to give a cumulative release of 91.17%, 87.61% and 81.02% respectively over a period of 24 h. Formulations F_6 and F_7 having the highest cholesterol content showed the slow release over 24 h, they provide a release of 77.63 % and 71.50% respectively as it is clearly visible in the Table.3 and Figure 6. The zero order plots showed the zero order release characteristics of the formulation, which was confirmed by the correlation value which found to be nearer to one. Correlation value of Higuchi's plot revealed that the mechanism of drug release is diffusion. The *in vitro* kinetic data subjected to log time log drug release transformation plot (peppa's model) revealed the fact that the drug release follows a super case II transport diffusion. Physical stability was carried out to investigate degradation effect of the lornoxicam from proniosomes at refrigerated temperature. The percentage of lornoxicam retained in the reconstituted vesicles after a period of three months were 94%, 98.07% and 97.69% respectively for formulations F_3, F_4 and F_5. Also the results indicate that more than 90% of lornoxicam was retained in the proniosomal formulation for a period of 90 days as it is shown in the Table 4 and Figure 7. From this it can be concluded that proniosomes are stable to store under refrigeration temperature with least leakage. The leakage of drug from F_6 and F_7 may be due to its lower surfactant content and higher cholesterol which formed a leaking vesicle. Proniosomes are prepared with non-ionic surfactant (span 60) and cholesterol by coating maltodextrin powder as carrier, which upon reconstitution gives niosomes. Lornoxicam, an antibacterial drug is encapsulated in these formulations for the sustained action of drug. On using different ratios, 170:80 µmol ratios of the surfactants to cholesterol preparation show the highest entrapment efficiency and good release characteristics. In this study it is found that entrapment efficiency of drug depends upon the cholesterol and surfactant ratio.

Figure 1: FT-IR Spectra of lornoxicam

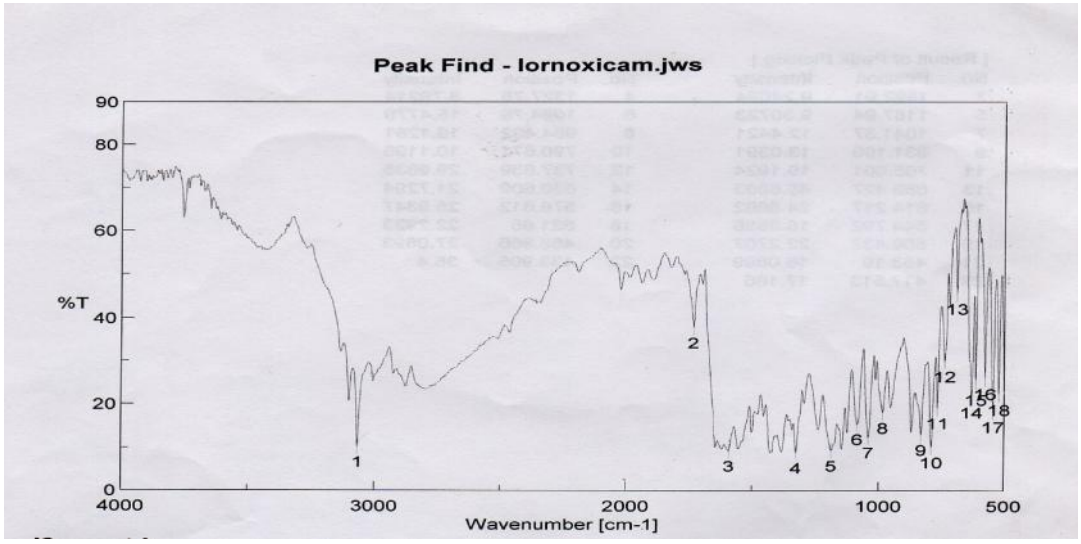


Figure 2: FT-IR Spectra of Maltodextrin

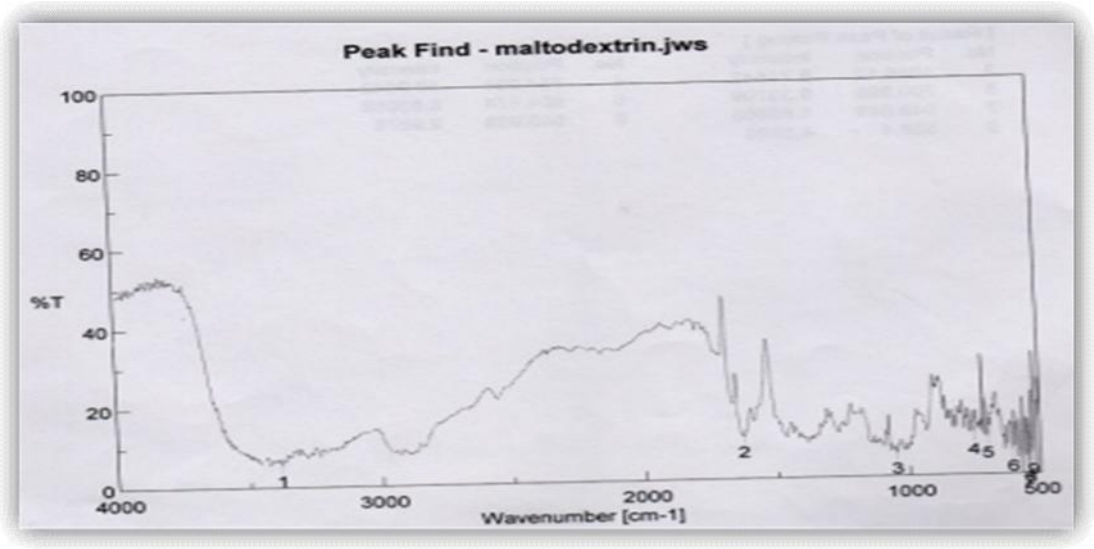


Figure 3: FT-IR Spectra of formulation

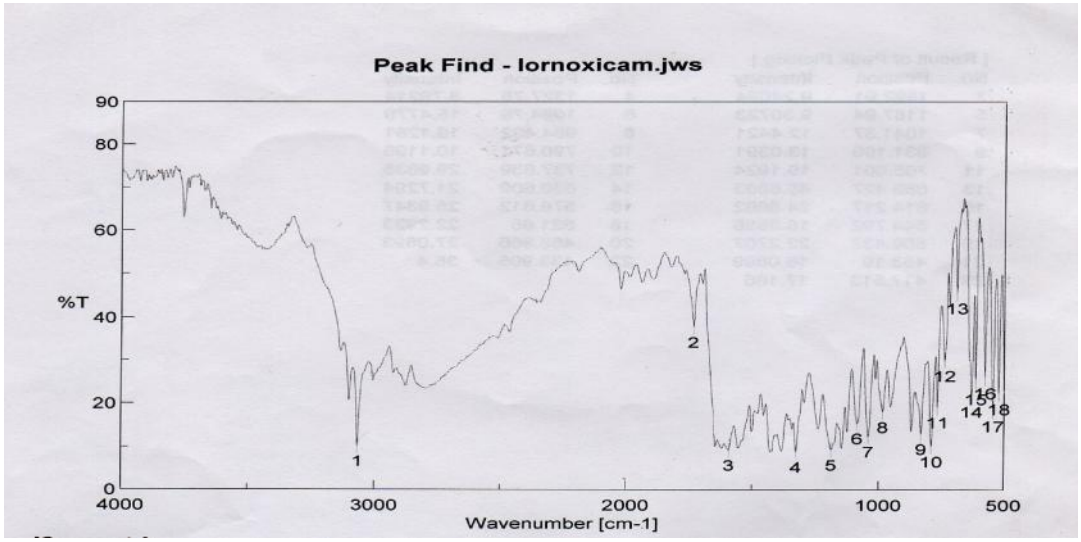


Figure 4: Scanning electron microscopy of best formulation

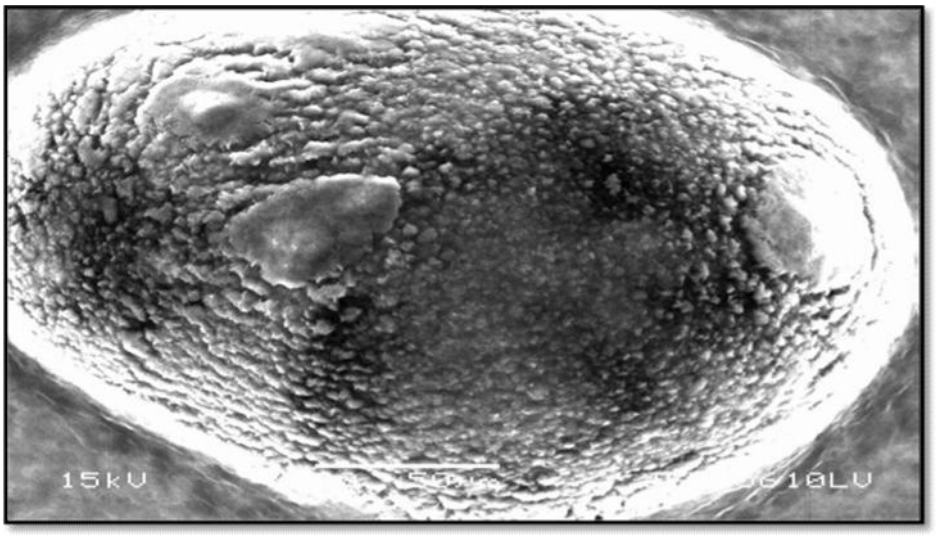


Figure 5: Photomicrograph of lornoxicam niosome in a dry glass slide

Table 1: Composition Of Proniosome Batches Of Lornoxicam And Result Of Entrapment Efficiency

Formulation	Ratio(µmol) (surfactant:cholesterol)	Entrapment efficiency %
F1	210:40	65.37%
F2	190:60	67.70%
F3	170:80	72.69%
F4	150:100	70.52%
F5	130:120	69.99%
F6	110:140	62.61%
F7	90:160	58.26%

Drug content used 15mg per batch
1mg of carrier per 1µmol of surfactant

Table 2: Result Of Angle Of Repose

Formulation	Angle of repose
Maltodextrin Powder	$45^0$19’
F1	$36^0$52’
F2	$33^0$69’
F3	$25^0$46’
F4	$31^0$21’
F5	$30^0$46’
F6	$26^0$56’
F7	$23^0$51’

Table 3: *In-vitro* release profile of all formulations

Formulation release	Time (In hrs)	Precentage drug
F1	24h	79.97
F2	24h	83.62
F3	24h	91.17
F4	24h	87.16
F5	24h	86.12
F6	24h	81.02
F7	24h	76.71

Figure 6: *In-vitro* release of all formulation

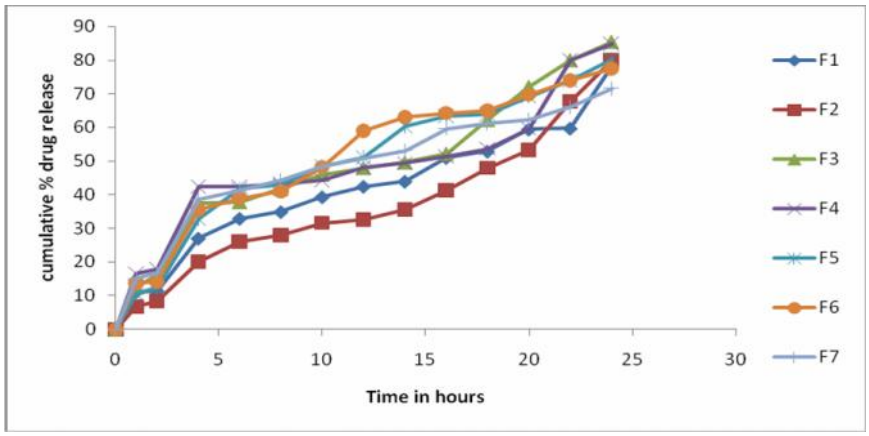
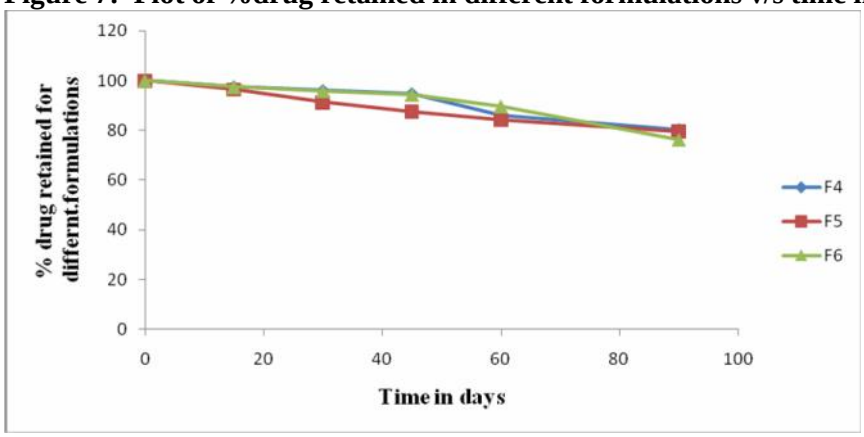


Table 4: Percentage of Lornoxicam retained on refrigerated storage

S.No	Days Stored	F3 % Retained	F4 % Retained	F5 % Retained
1	0	100	100	100
2	15	97.44	96.42	98.92
3	30	97.44	91.30	95.77
4	45	94.71	87.58	94.39
5	60	85.84	84.19	89.65
6	90	80.13	79.55	76.55

Figure 7: Plot of %drug retained in different formulations v/s time in days



Conclusion

Compared to liposome or niosomes, proniosomes are very promising as drug carriers. Proniosome represents a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drug's during long term storage. Proniosome are convenient to store, transport and for unit dosing since proniosome's have similar release characteristics as conventional niosomes, it may offer improved bioavailability of some drugs with poor solubility, controlled release formulations or reduced adverse effects of some drugs. Because proniosome are a dry powder, further processing is possible. To provide convenient unit dosing, the proniosome powder may be processed to make beads, tablets or capsules. The hydration of proniosome powder is much easier than the long shaking process required hydrating surfactant in the conventional dry film method. Proniosome derived niosome suspension is found to be as good or better than conventional niosome preparation; and may be an appropriate preparation to use as a hydrophilic drug carrier. By these facts of the study it is concluded that lornoxicam will be successfully entrapped within the bilayer of the vesicles with high entrapment efficiency and said that proniosomes based niosomes formed from span 60, cholesterol using maltodextrin as a carrier is a promising approach to sustain the drug release for an extended

period of time and thus reducing the side effects related to GI irritation. The slurry method was found to be simple and suitable for laboratory scale.

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