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Meloxicam loaded proniosome of different carrier for better by oral delivery

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Abstract
Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Maltodextrin and Mannitol has been used as carriers for the preparation of Various Proniosome powder formulations by slurry method. Niosomes derived from Proniosomes of both carriers were compared in terms of morphology, vesicle size, entrapment efficiency and in vitro drug release. Meloxicam used as model drug. Average particle was found to be in range of 6.943 to 7.258 µm for Maltodextrin and from 5.919 to 7.026 µm for Mannitol. Percentage cumulative drug release was higher in maltodextrin as compared to mannitol while entrapment efficiency was less in Mannitol as compared to Maltodextrin. Thus it can be concluded that Mannitol can be used as suitable carrier for preparation of proniosomes.

Keywords: proniosome, maltodextrin, mannitol and span 60

1. Introduction
Novel drug delivery attempts to either sustain drug action at a predetermined rate, or by maintaining a relatively constant, effective drug level in the body with associated minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type. Recently, different carrier systems and technologies have been extensively studied with aim of controlling the drug release and improving the efficacy and selectivity of formulation. Now-a-days, the vesicular systems like liposomes or niosomes have specific advantages while avoiding demerits associated with conventional dosage forms. To overcome the disadvantage of vesicular system, Proniosomes are designed [1].

Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing [2].

Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of Proniosome-derived niosomes are somewhat better than those of conventional niosomes so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the Proniosome powder is provided could be beneficial [3].

Meloxicam is a nonsteroidal anti-inflammatory drug of the Oxicam class, used to relieve the symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component8. Meloxicam inhibits cyclooxygenase (COX) synthesis. This enzyme is responsible for converting arachidonic acid into prostaglandin H2. This is the first step in the synthesis of prostaglandins, which are mediators of inflammation. Meloxicam has been shown, especially at its low therapeutic dose, selectively to inhibit COX-2 over COX-1 9. A primary advantage of the Oxicam family of drugs is their long half-life which permits once-day dosing (10). In gastric disease, lower dose of meloxicam is required 7.5 mg/day. Meloxicam is safer than other NSAID's [4, 5].

2. Material and Method
Meloxicam obtained as a gift sample Dr. Reddy's Pharmaceutical Ltd, Hyderabad, India maltodextrin, Mannitol, Cholesterol and span-60 were purchased from S.D Fine Chem Limited, Mumbai. All other reagents used were of analytical grade.

2.1 Preparation of proniosome by using (maltodextrin and mannitol) as carrier [7, 9]
Proniosomes were prepared by the slurry method. For ease of preparation, a 250µmol stock solution of span-60 and cholesterol was prepared in chloroform: methanol (2:1) solution. The required volume of span-60, cholesterol stock solution and drug dissolved in chloroform: methanol (2:1) solution was added to a 100ml round bottom flask containing the maltodextrin/Mannitol carrier. Additional chloroform: 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 ± 2 ℃, and a reduced pressure of 600 mmHg until the mass in the flask had become a dry, free flowing product. 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.

Table 1: Formulation of proniosome powder,

formulation code	Drug	Cholesterol	Span 60	Maltodextrin	Mannitol
MDX1	50	100	100	500	-
MDX2	50	100	200	500	-
MDX3	50	100	300	500	-
MTL1	50	100	100	-	500
MTL2	50	100	200	-	500
MTL3	50	100	300	-	500

3. Evaluation parameter [6, 14]

Formulation of Proniosome powder can be evaluated by FT-IR, Angle of repose, particle size analysis, zeta potential, SEM, Entrapment efficiency and in *vitro* drug release

3.1 *In Vitro* drug release studies

The release of drug was determined by using the treated cellophane membrane mounted on the one end of open tube, containing proniosomes (equivalent to 50 mg Meloxicam). The dialysis tube was suspended in 500 ml beaker, containing 250 ml of 0.1N NaoH solution. The solution was stirred at 100 rpm with the help of magnetic stirrer at 37 ± 0.5 ℃. Perfect sink conditions were maintained during the drug release testing. The samples were withdrawn at suitable time interval (at 1, 2, 3, 4, 8, and 12 hrs.). The dissolution medium was replaced with same amount of fresh 0.1N NaOH solutions to maintain the volume 250 ml throughout the experiment. The drug content in the withdrawn samples (5 ml) were analyzed by UV spectrophotometer at λmax 362 nm and cumulative % of drug released was calculated and plotted against time (t). The rate and release mechanism of Meloxicam from the prepared proniosomes were analyzed by fitting the release data in to various kinetic models.

FT-IR Studies

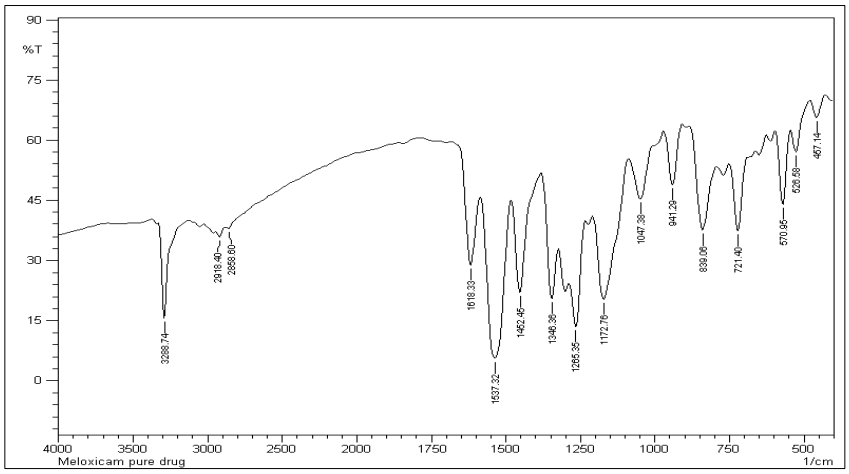

Fig 1: FT-IR spectrum for pure Meloxicam

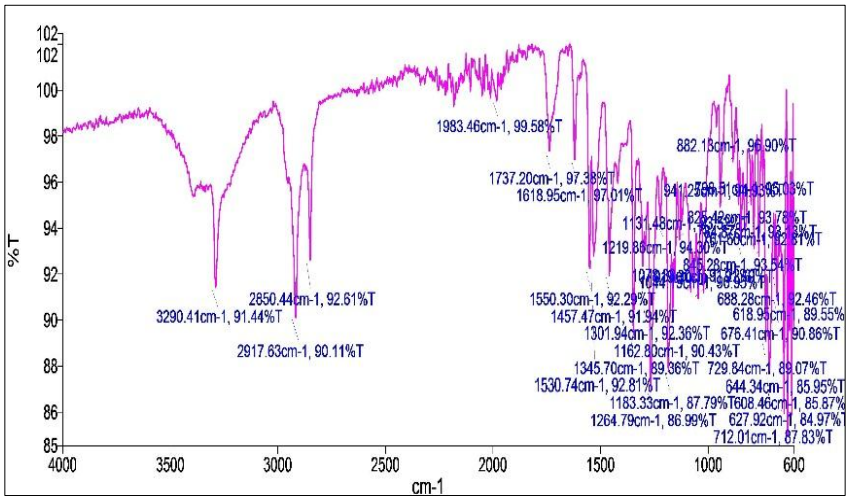

Fig 2: FT-IR Spectroscopy of proniosome F3

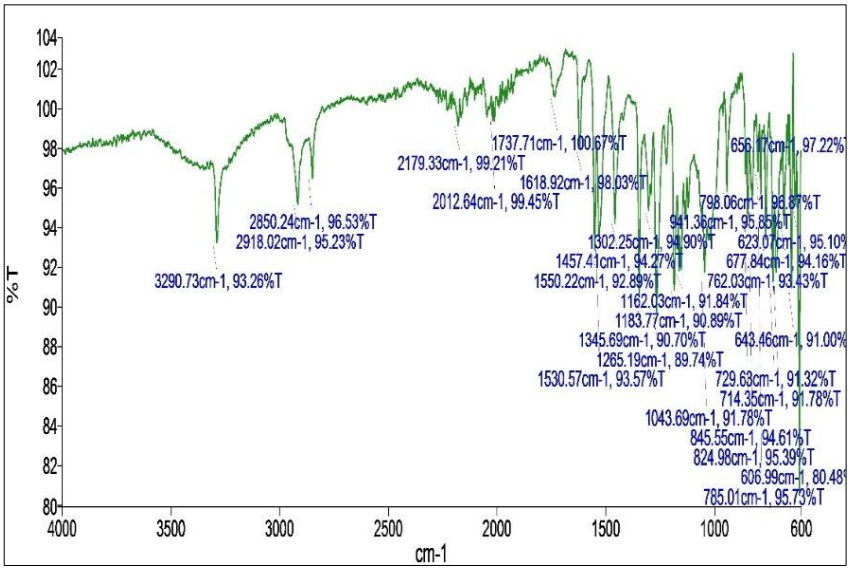

Fig 3: FT-IR Spectroscopy of proniosome F6

Table 2: angle of repose

Preparation	Angle of repose
Maltodextrin	40˚ 52
F1	38˚.52
F2	36˚.45
F3	34˚.36
Mannitol	25˚.15
F4	24˚.56
F5	23˚.12
F6	22˚.42

Table 3: Average particle size and Entrapment efficiency

Formulation code	Average particle size in µm	% Entrapment efficiency
F1	6.943	74.22
F2	7.077	76.88
F3	7.258	77.18
F4	5.919	71.21
F5	6.451	72.86
F6	7.026	73.24

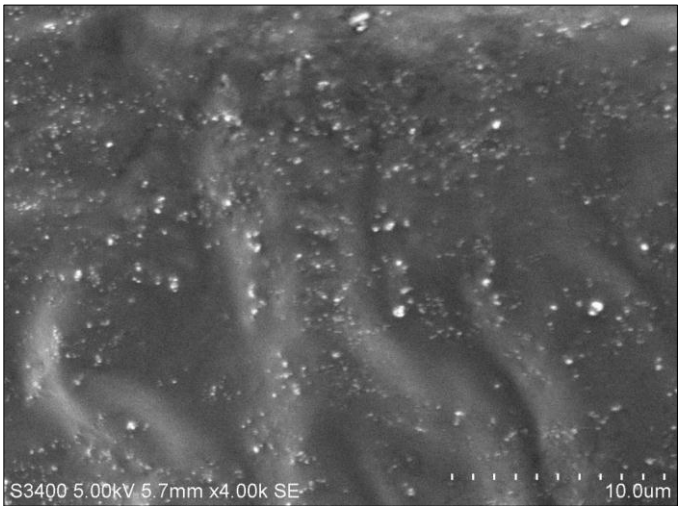

Fig 4: Scanning electron microscopy for optimized F2 formulation

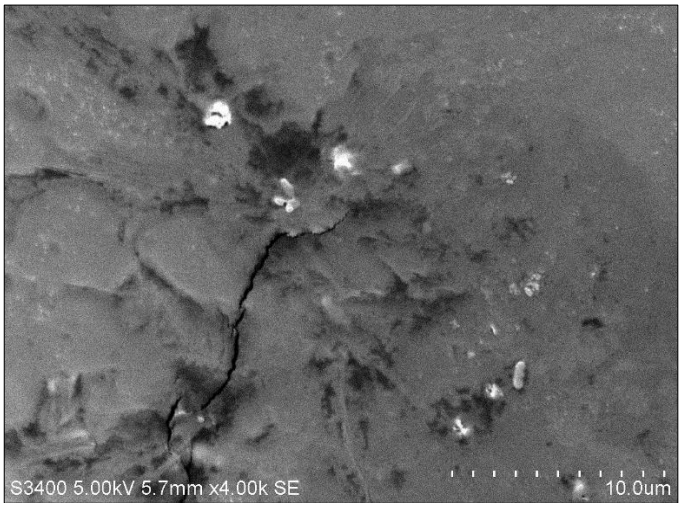

Fig 5: Scanning electron microscopy for optimized F5 formulation

Particle size analysis

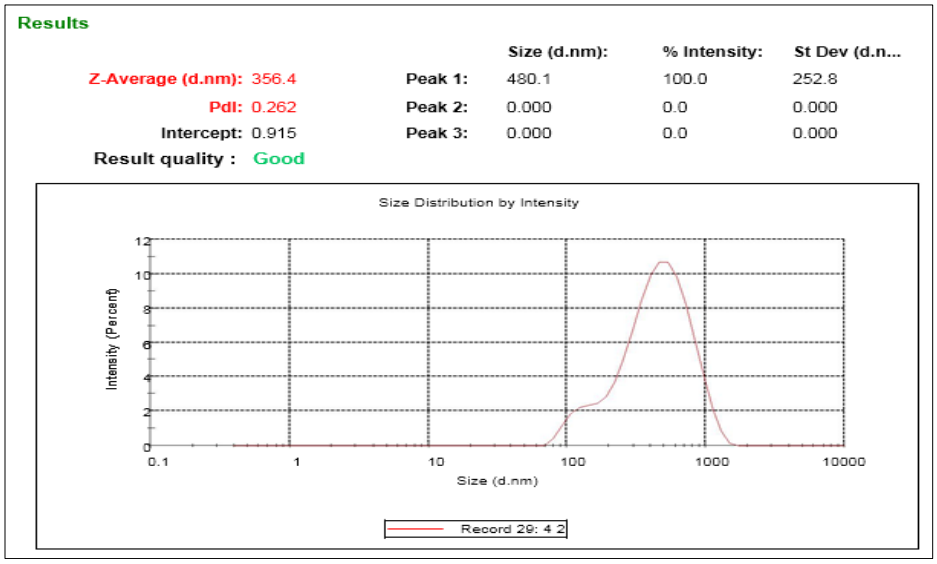

Fig 6: Particle size data for optimized proniosomes formulation F2

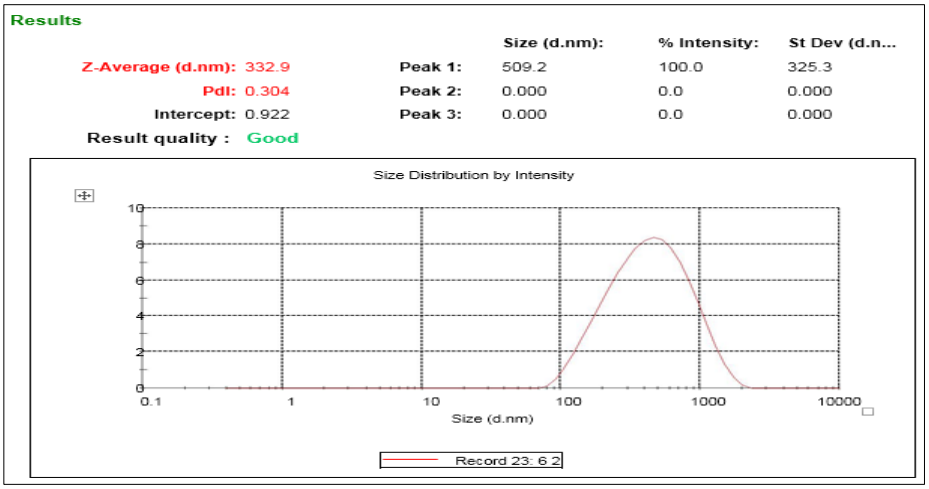

Fig 7: Particle size data for optimized proniosomes formulation F5

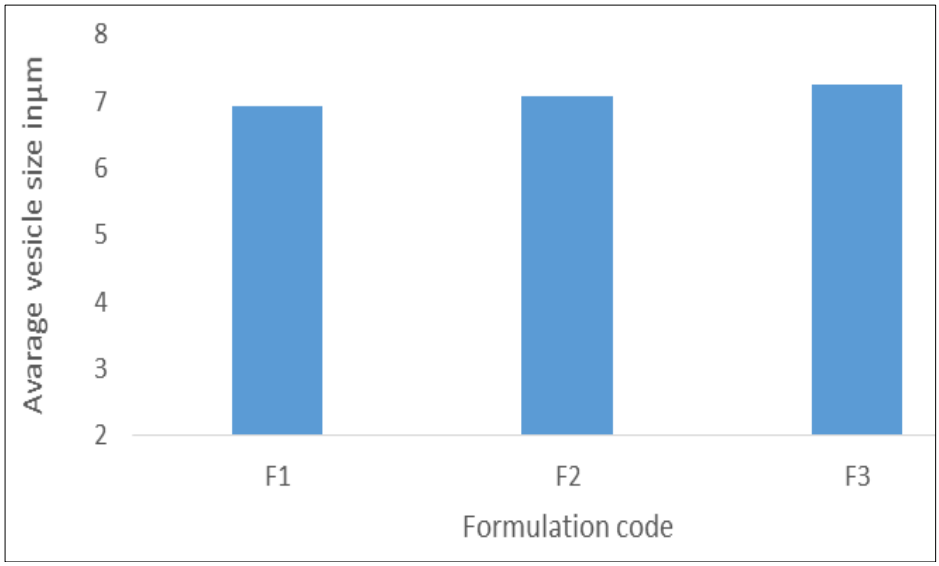

Fig 8: Average vesicle size range of proniosomes formulation from F1-F3

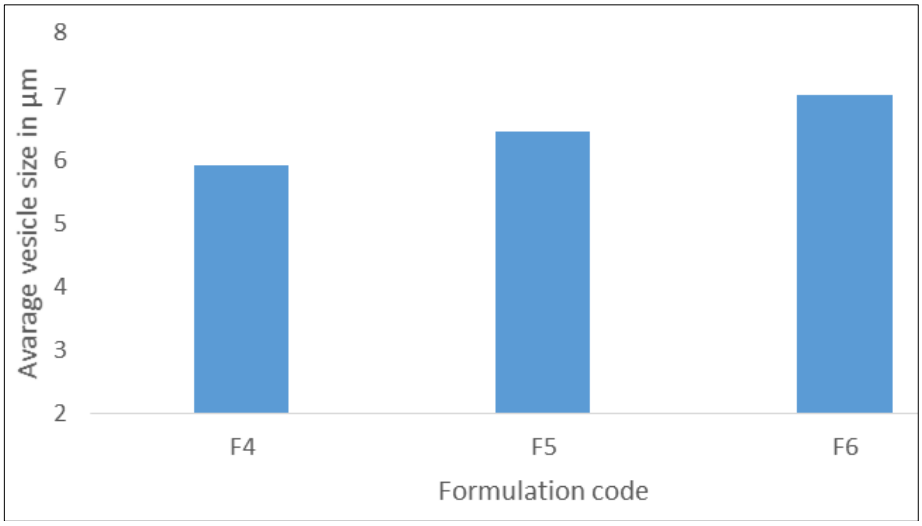

Fig 9: Average vesicle size range of proniosomes formulation from F4-F6

Zeta Potential

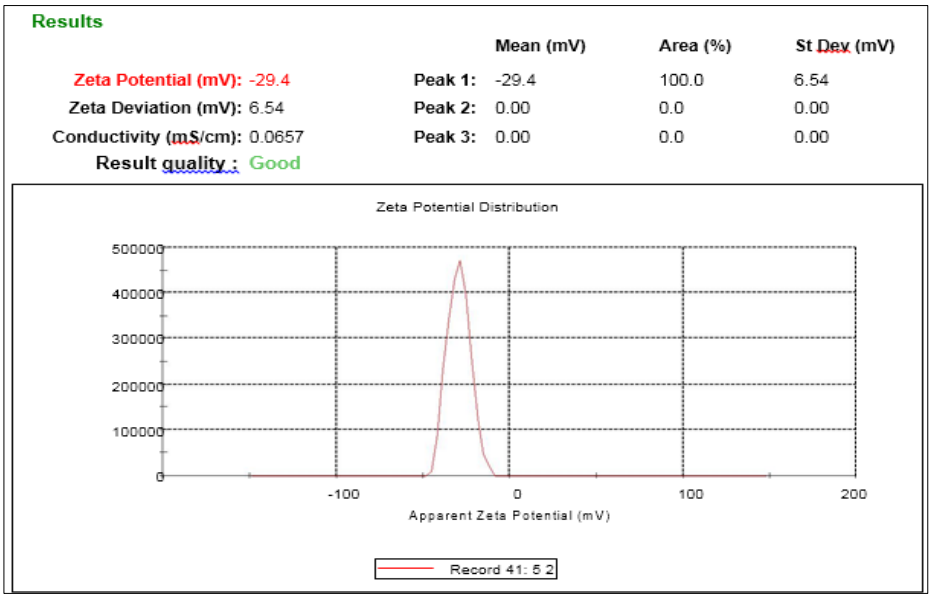

Fig 10: Zeta potential of optimized proniosomes formulation F2

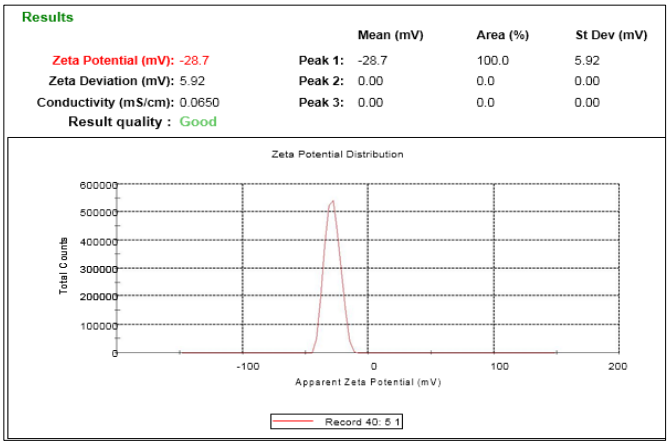

Fig 11: Zeta potential of optimized proniosomes formulation F5

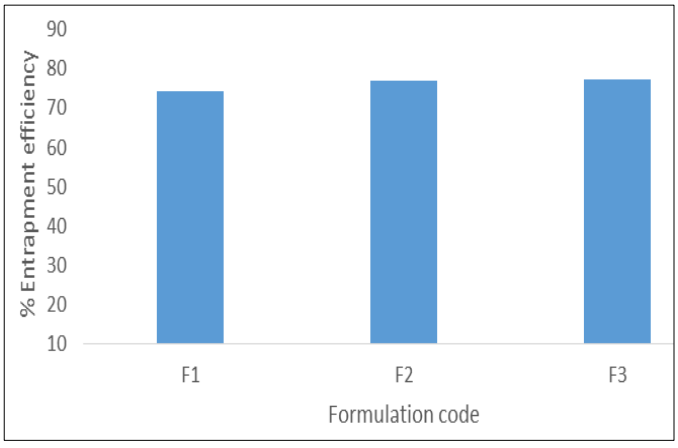

Fig 12: Entrapment efficiency of proniosome formulation F1 – F3

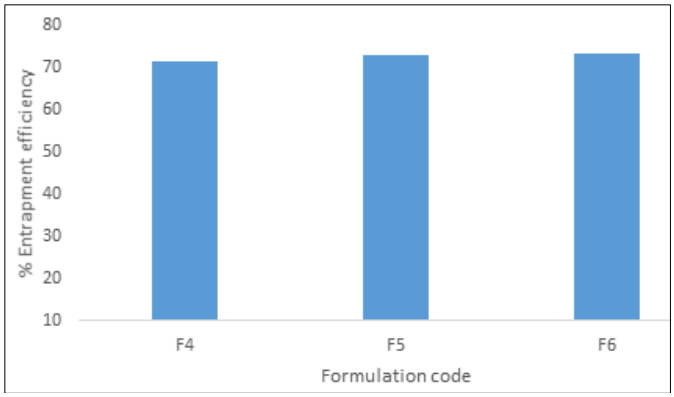

Fig 13: Entrapment efficiency of proniosome formulation F4 – F6

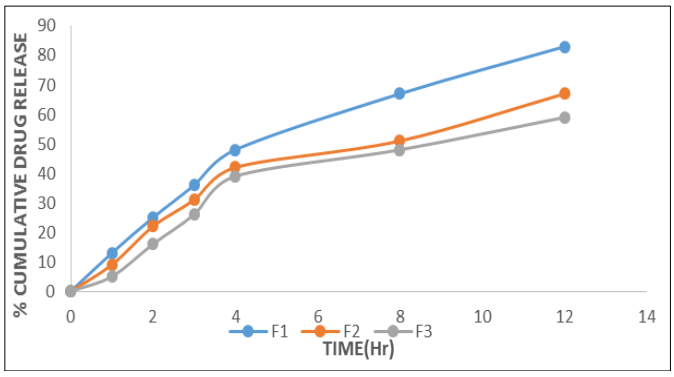

Fig 14: % Cumulative drug release of proniosomes formulation from F1-F3

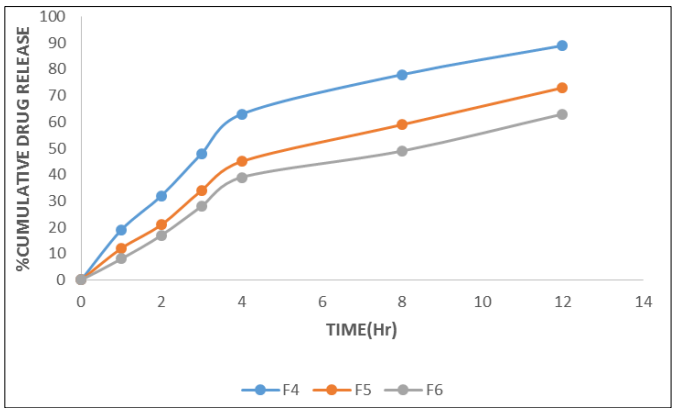

Fig 15: % Cumulative drug release of proniosomes formulation from F4-F6

4. Result and Discussion

Proniosome containing Meloxicam was prepared using non-ionic surfactant span 60 and cholesterol in different proportions slurry method.

In FT-IR study, the characteristic peaks due to pure Meloxicam have appeared in proniosome formulation, without any mark able change in their position after successful encapsulation, indicating no chemical interaction between drug and carrier. The result shows in (fig 1, 2 and 3).

The angle of repose of dry proniosome powder is smaller than that of pure carrier like maltodextrin and mannitol. Maltodextrin containing formulation (F1, F2 and F3) shows higher angle of repose than the mannitol containing formulation (F4, F5 and F6) and results are reported in Table 2.

Shape and surface characteristic of proniosome was examined by Scanning Electron Microscopy analysis. Meloxicam loaded Maltodextrin and Mannitol Proniosome (F2 and F5 formulation) are evaluated for surface morphology. Surface morphology confirms the coating of surfactant in carrier as shown Fig 4 and 5. Some unevenness of vesicles that observed under the study may be due to drying process under normal environment condition. The prepared vesicles are studied by optical microscope under 10X magnifications to observe the formation of vesicles. Nearly 300 particle size were measured and the average vesicle size were reported in Table no 3 and Fig 8 and 9

The mean particle size for optimized formulation F2 and F5 were studied by Malvern particle size analyzer found in the range of 356.4 nm 332.9 nm.it shows in the fig 6 and 7 it indicates maltodextrin shows high mean particle size when compared to mannitol. And zeta potential analysis for F2 and F5 by using Malvern zeta analyzer which gives the negative value of –28.7 mV, –29.4 mV. And reported in fig 10 and 11

Entrapment efficiency was studied for all the 6 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 with the formulation F3 (80.16 %) with maltodextrin and F6 (73.24 %) with mannitol which may higher entrapment efficiency which might be due to the high fluidity of the vesicles. From this maltodextrin shows high entrapment efficiency when compared to mannitol. It shows in table 3 and fig 12 and 13

The release study was conducted for all the 6 formulation. Most of the formulation were found to have a linear release. The two best formulations maltodextrin and mannitol (F3 and F6) were found to give a cumulative drug release of 63 % and 59 % respectively over a period of 12 hrs. It indicating still drug remain in the niosomes after12hrs. From this mannitol shows less drug release compared to maltodextrin. It reported in fig 13 and 14

The *in vitro* release data was applied to various kinetic models like zero order kinetics, Higuchi's plot and Peppa's plot to predict the drug release kinetic mechanism. Therefore, it was ascertained that the drug release. Higuchi's plot were in between 0.9679to 0.9599 which revealed that the mechanism of drug release is diffusion. Korsmeyer-Peppa's plot slope values ranges from 0.6698 to 0.7652 which revealed the fact that the drug release follows nonfiction diffusion.

5. Conclusion

Proniosomes consist of dry, free flowing powder which on hydration forms multilamellar niosomal suspension, suitable for administration by oral and other routes.. In the present investigation proniosomes were prepared using mannitol as a carrier and compared with maltodextrin based proniosomes. Meloxicam was used a model drug. Proniosomes of mannitol and maltodextrin were prepared by slurry method. Niosomes were prepared from proniosomes by hydrating proniosome powder. Niosomes, so obtained were characterized for morphology, entrapment efficiency and in vitro release. SEM images of mannitol and maltodextrin indicates that maltodextrin is covered by a thick layer or surfactant while mannitol proniosomes show a thin covering of surfactant. Average particle was found to be in range of 6.943 µm to

7.258 µm for maltodextrin and from 5.919 µm to 7.026 µm for mannitol. Percentage cumulative drug release was higher in maltodextrin as compared to mannitol while entrapment efficiency was less in Mannitol as compared to maltodextrin.. So it can be concluded that maltodextrin is a good carrier compared to mannitol. But mannitol can also be used as suitable carrier for the preparation of proniosomes.

6. References

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