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PRONIOSOMES FOR ORAL DELIVER OF MELOXICAM: FORMULATION AND IN VITRO EVALUATION

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ABSTRACT
Meloxicam loaded sorbitol and mannitol based proniosome were prepared by slurry method with different surfactant ratio. The proniosome formulation was evaluated for FT-IR study and scanning electron microscopy. The niosomal dispersion was further evaluated for entrapment efficiency, *in-vitro* release study, kinetic data analysis, stability study. The result from SEM analysis has showed smooth surface of proniosome. The formulation FS3 and FM3 which showed entrapment efficiency 77.18% and 73.24% respectively. *In vitro* cumulative drug release 59% and 62% respectively at the end of 12 hrs. Release kinetic was found to be best among the all 6 formulations. Release was best explained by the higuchi model. Kinetic analysis showed that the drug release follows non-fickian release.

KEYWORD: Meloxicam, Proniosome, sorbitol and mannitol.

INTRODUCTION
In recent past, proniosomes have gained considerable attention owing to their higher efficiency in manufacturing and formulation stability compared to other vesicular carrier like liposomes and niosomes.[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 niosome physical stability such as aggregation, fusion and leaking and provide additional convenience in transportation, distribution, storage, dosing, and make proniosomes a versatile delivery system with potential for use with a wide range of active compounds. Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes. In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes.[2, 3]

Meloxicam is in a class of medications called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by stopping the body's production of a substance that causes pain, fever, and inflammation. Meloxicam is most commonly used in chronic musculoskeletal pain management, and degenerative inflammatory diseases such as osteoarthritis and rheumatoid arthritis.[5] Currently, it is available only as oral tablets and various attempts were made to formulate Meloxicam in other forms for optimal pain management.[4] Meloxicam is poorly soluble drugs and it may cause ulcers bleeding, or holes in the stomach or intestine. These problems may develop at any time during treatment, may happen without warning symptoms, and may cause death.

Therefore, Meloxicam needs to be carefully extended for other oral therapies that would need fast and efficient absorption to achieve rapid onset pharmacological activity such as migraine attacks and other acute pain management. The above observation should provide impetus for the development of superior oral formulation *via* the application of novel technologies.[5,6]

Hence, the main objective of this study is to formulate proniosomal Meloxicam for oral delivery to improve the solubility, to increase the bioavailability and to minimize the problem associated with conventional Meloxicam dosage form.

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

Preparation of proniosome by using (sorbitol 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 Sorbitol/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	Sorbitol	Mannitol
FS1	50	100	100	500	-
FS2	50	100	200	500	-
FS3	50	100	300	500	-
FM1	50	100	100	-	500
FM2	50	100	200	-	500
FM3	50	100	300	-	500

EVALUATION PARAMETER[10, 15]

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 as per standard procedure reported in literature.

***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

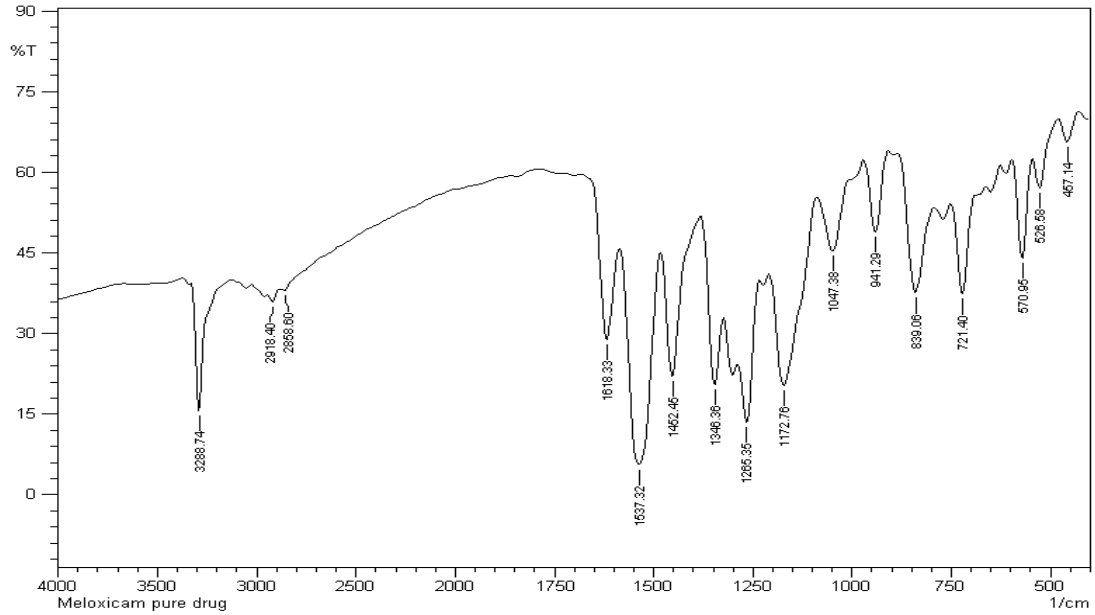

Fig 1: FT-IR spectrum for pure Meloxicam.

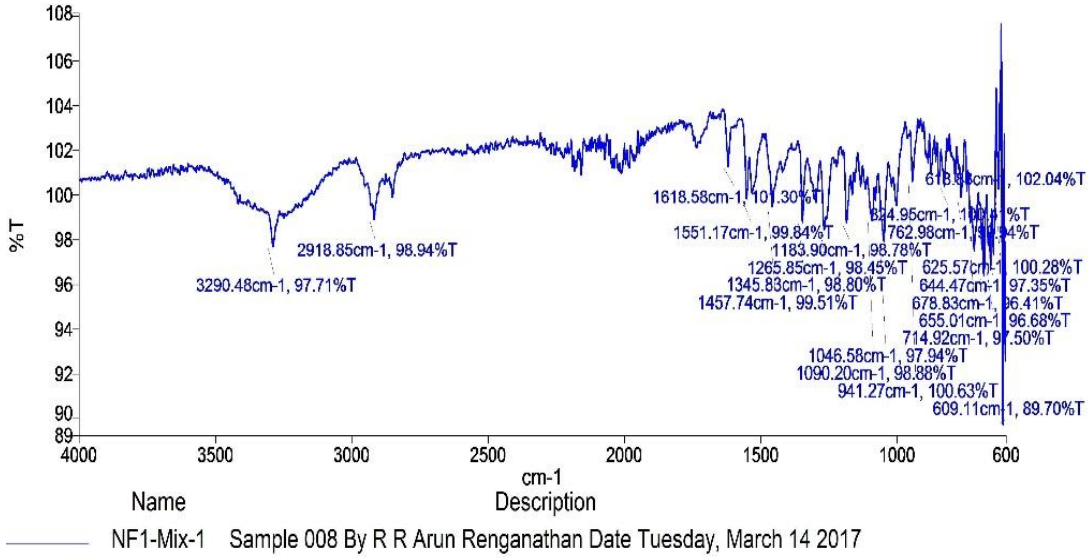

Fig 2: FT-IR Spectroscopy of proniosome FS3.

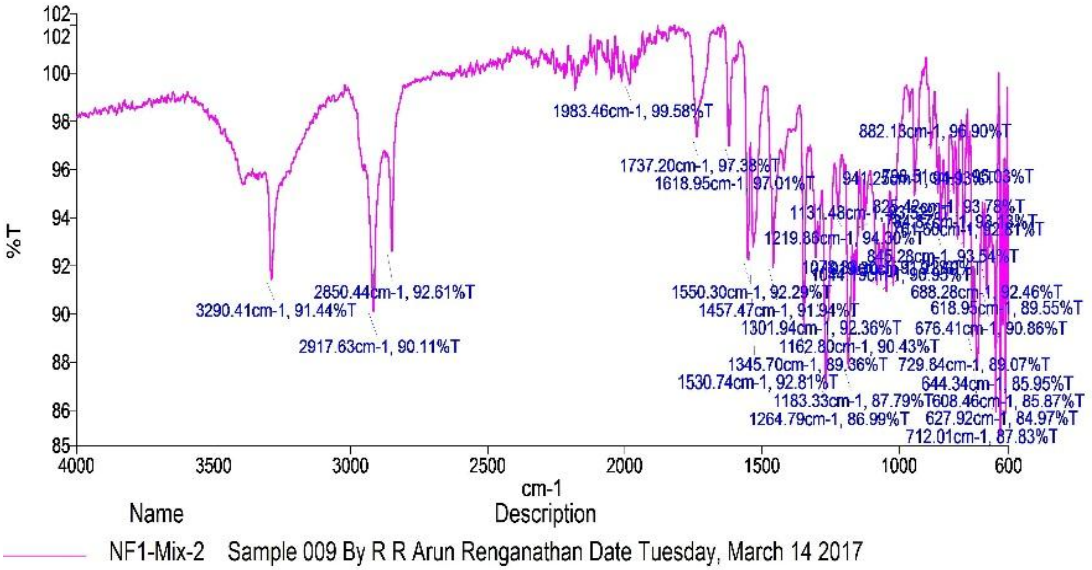

Fig 3: FTIR Spectroscopy of Proniosomes FM2.

Table 2: Angle of repose.

Preparation	Angle of repose
Sorbitol	31°.25
FS1	30°.50
FS2	28°.81
FS3	27°.36
Mannitol	25°.15
FM1	24°.56
FM2	23°.12
FM3	22°.42

Table 3: Average particle size and entrapment efficiency

Formulation code	Average particle size in µm	% Entrapment efficiency
FS1	5.919	74.22
FS2	6.451	76.88
FS3	7.026	77.18
FM1	5.977	71.21
FM2	6.246	72.86
FM3	6.643	73.24

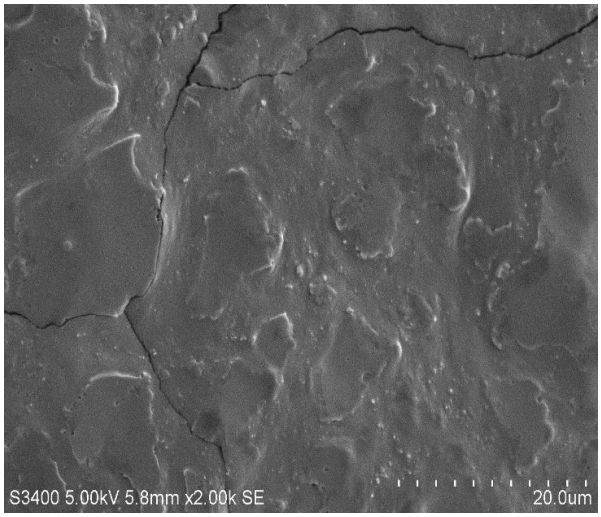

Fig 4: Scanning electron microscopy for optimized FS2 formulation

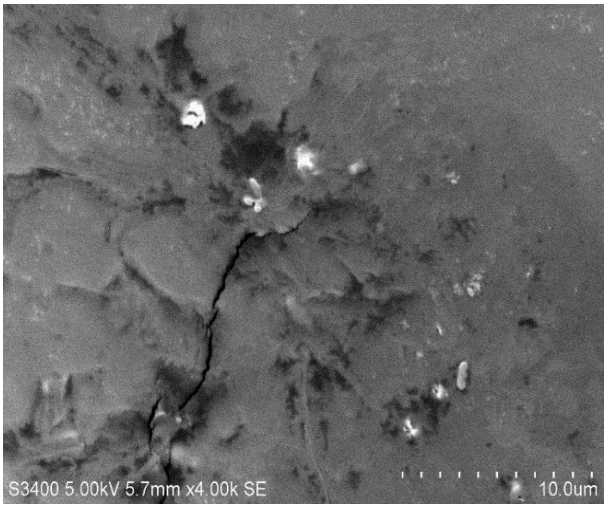

Fig 5: Scanning electron microscopy for optimized FM2 formulation

Particle size analysis

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 323.9	Peak 1:	467.1	100.0	260.4
PdI: 0.293	Peak 2:	0.000	0.0	0.000
Intercept: 0.912	Peak 3:	0.000	0.0	0.000

Result quality : Good

Fig 6 : Particle size data for proniosomes formulation FS2.

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 332.9	Peak 1:	509.2	100.0	325.3
PdI: 0.304	Peak 2:	0.000	0.0	0.000
Intercept: 0.922	Peak 3:	0.000	0.0	0.000

Result quality : Good

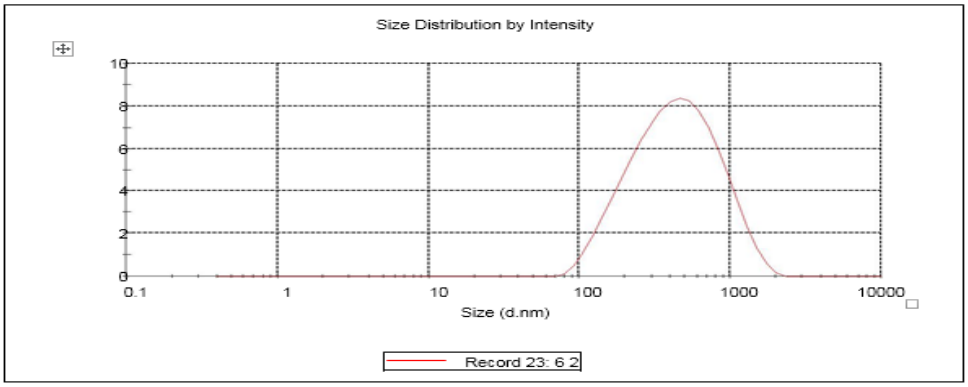

Fig 7: Particle size data for proniosomes formulation FM2.

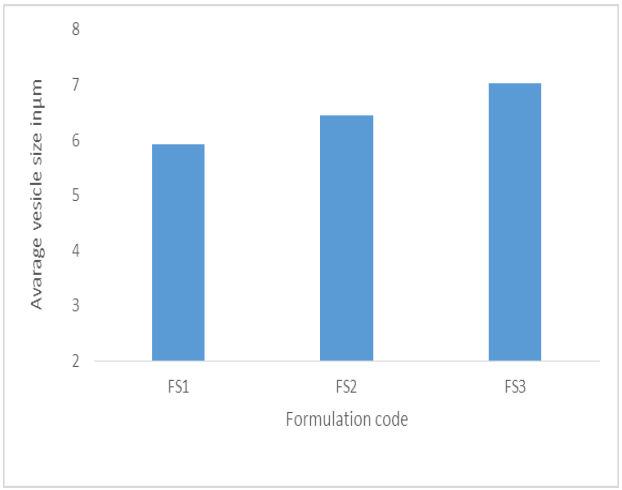

Fig 8: Average vesicle size range of proniosomes formulation from FS1-FS3.

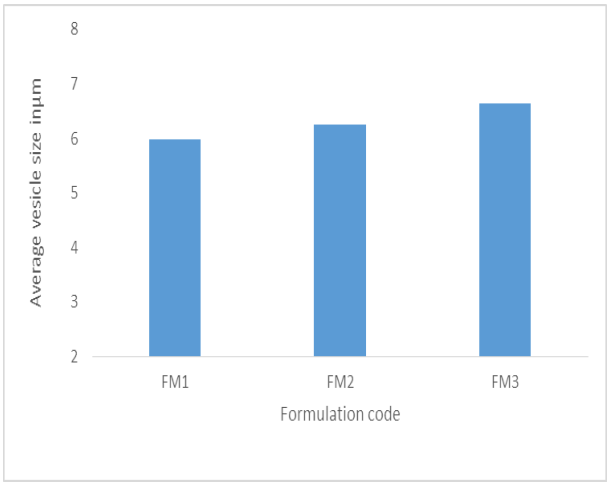

Fig 9: Average vesicle size range of proniosomes formulation from FM1-FM3

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -28.7	**Peak 1:**	-28.7	100.0	5.92
Zeta Deviation (mV): 5.92	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.0650	**Peak 3:**	0.00	0.0	0.00
Result quality : Good				

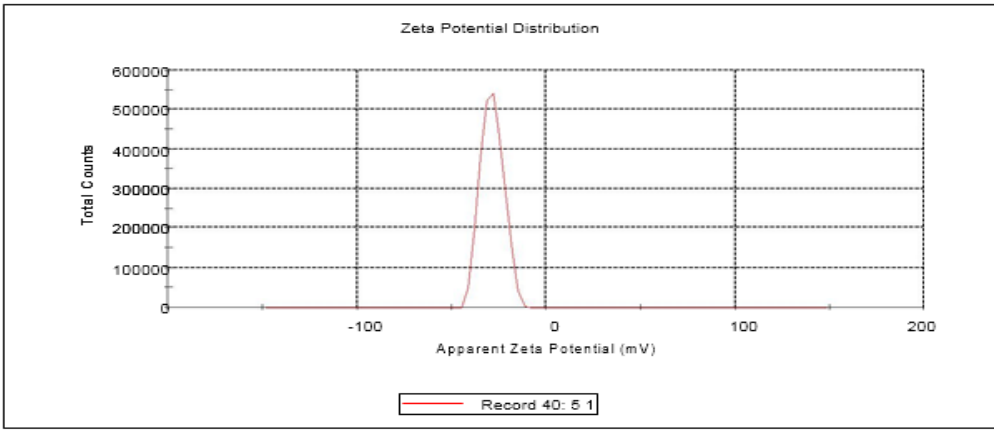

Fig 10: Zeta potential of optimized proniosomes formulation FS2.

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -27.7	**Peak 1:**	-27.7	100.0	5.64
Zeta Deviation (mV): 5.64	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.0663	**Peak 3:**	0.00	0.0	0.00
Result quality : Good				

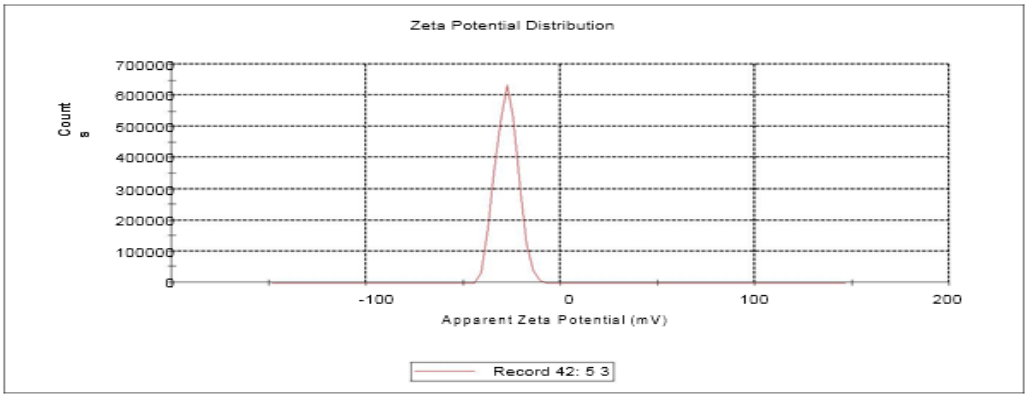

Fig 11: Zeta potential of optimized proniosomes formulation FM2

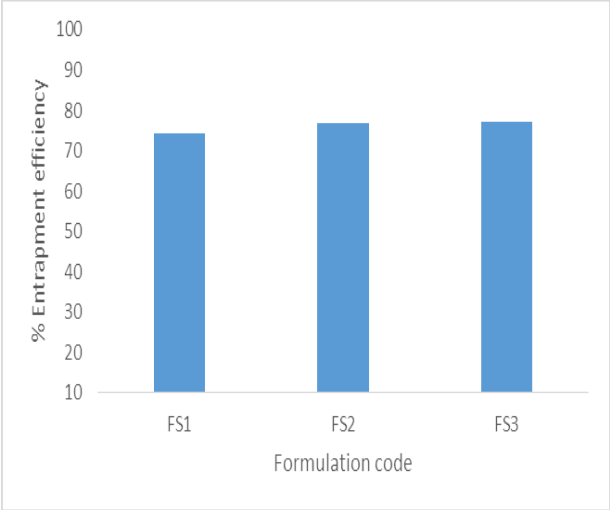

Fig 12 Entrapment efficiency of proniosome formulation FS1 – FS3

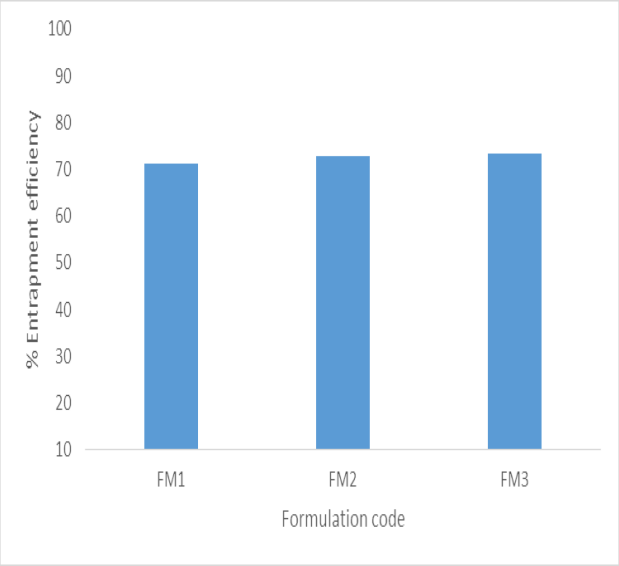

Fig 13: Entrapment efficiency of proniosome formulation FM1 – FM3.

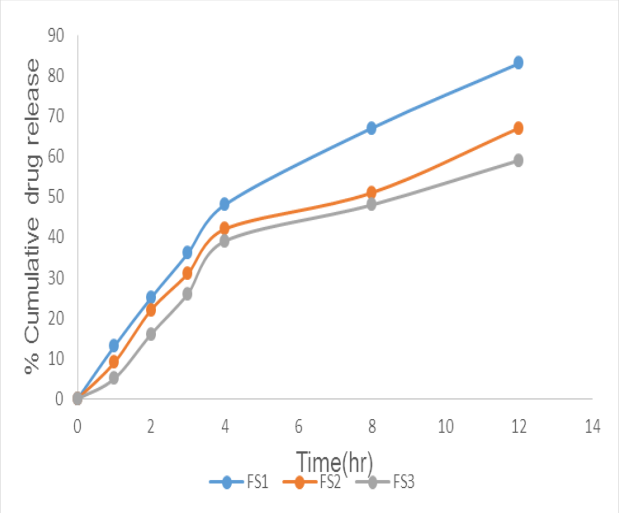

Fig 13: % Cumulative drug release of proniosomes formulation from FS1-FS3

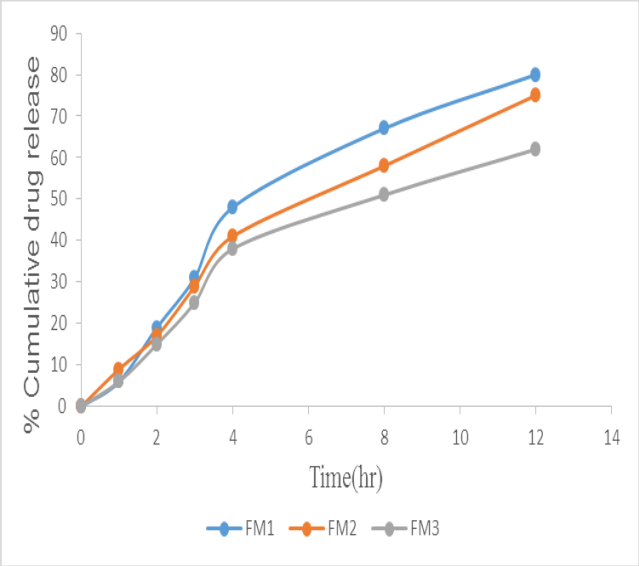

Fig 14: % Cumulative drug release of proniosomes formulation from FM1-FM3

RESULT AND DISCUSSION

FT-IR Spectra of Meloxicam, Sorbitol, Mannitol, physical mixture of drug carrier and FS3 and FM3 formulation were recorded. The Meloxicam present in the formulation FS3and FM3 was confirmed by FTIR spectra. The characteristic peaks due to pure Meloxicam at 3288.74, 2918.40, 2858.60, 1537.32 $cm^{-}1$. All these peaks have appeared in, indicating no chemical interaction between Meloxicam and carriers. The results are shown in fig 1, 2 and 3.

Angle of repose of Sorbitol and Mannitol powders compared with proniosome formulation by fixed funnel method. Results indicate that the angle of repose of dry proniosome powder is nearly equal to that of pure carrier, like sorbitol and mannitol. This shows that the prepared proniosome formulations have appreciable flow properties. Sorbitol as more angle of repose when compared to mannitol and the results ared reported in table 2.

Shape and surface characteristic of proniosome was examined by Scanning Electron Microscopy analysis. Meloxicam loaded Sorbitol and Mannitol Proniosome (FS2 and FM2 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 FS2 and FM2 werestudied by Malvern particle size analyzer and mean particle size are found in the range of 332.9 nm 323.9 nm as shown in fig 6 and 7. Zeta potential

analysis were done for FS3 and FM3 by using Malvern zetaanalyzer and found the value lied of –28.7 mV, –27.7 mV respectively which confirmed the stability of vesicles and the zeta analysis are 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 no. FS3 (77.18%) with sorbitol and FM3 (73.24%) with Mannitol which may higher entrapment efficiency which might be due to the high fluidity of the vesicles. There are reports that entrapment efficiency was increased, with increasing concentration of surfactant (span-60). The larger vesicle size may also contribute to the higher entrapment efficiency. The carrier also plays a vital role as we can see directly from the data there is high entrapment efficiency with sorbitol as compared to mannitol. It reported in table 3 and shows in Fig 12 and 13.

The release study was conducted for all the 6 formulation. Most of the formulation was found to have a linear release. The two best formulations FS3 and FM3 were found to give a cumulative drug release of 59 % and 62 % respectively over a period of 12 hrs. It indicating still drug remain in the niosomes after12hrs as 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 0.9679 to 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 nonfickion diffusion.

CONCLUSION

On conclusion, this novel drug delivery system i. e. proniosome as compared to liposome or niosome represent a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drugs during long-term storage. Proniosomes derived niosomes are found to be superior in their convenience of storage, transport, and dosing as compare to niosomes and liposomes prepared by conventional method. By these facts of the study it is concluded that Meloxicam 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 sorbitol and mannitol as a carrier is a promising approach to sustain the drug release for an extended period of time and by that reducing the side effects related to GI irritation. The slurry method was found to be simple and suitable for laboratory scale preparation of Meloxicam proniosomes and this system also used to overcome the solubility problem associated with Meloxicam. Sorbitol - based proniosomes is a potentially scalable method for producing niosomes for delivery of hydrophobic or amphiphilic drugs when compared mannitol based proniosome. The method is simple and overcomes several problems encountered in previous studies. The niosomes produced using this method is effective carriers for amphiphilic drugs.

REFERENCE

1. Vasistha P, Ram A. Non-ionic provesicular drug carrier: an overview. Asian J Pharm Clin Res, 2013; 6(1): 38-42.
2. Sankar V, Ruckmani K, Durga S, Jailani S. Proniosomes as drug carriers. Pak J Pharm Sci, 2010 Jan 1; 23(1): 103-7.
3. Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. Int J Pharm, 1999 Aug 5; 185(1): 23-35.
4. Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, Bégaud B, et al. Gastrointestinal tolerability of Meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment. Br. J. Rheumatol, 1998; 37: 937-945.
5. Cetin EO, Buduneli N, Atlihan E, Kirilmaz L. *In vitro* studies of a degradable device for controlled-release of Meloxicam. J .Clin. Periodontol. 2005; 32: 773-777.
6. Auvinet B, Ziller R, Appelboom T, Velicitat P. Comparison of the onset and intensity of action of intramuscular Meloxicam and oral Meloxicam in patients with acute sciatica. Clin. Ther, 1995; 17: 1078-1098.
7. Goud BA, Raju J, Rambhau D. Improved Oral Absorption of Carbamazepine from Sorbitan Monolaurate based Proniosome Systems containing Charged Surface Ligands. Int J Biol Pharm Res, 2012; 3: 37-42.
8. Akhilesh D, Faishal G, Kamath JV. Comparative study of carriers used in proniosomes. Int J Pharm Chem Sci, 2012; 1(1): 164-173.
9. Akhilesh D, Faishal G, Prabhu P, Kamath DJ. Development and optimization of proniosomes for oral delivery of Glipizide. Int J Pharm Pharm Sci, 2012; 4(3): 307-14.
10. Parthibarajan R, Rubinareichal R, Loganathan S. Formulation and evaluation of Methotrexate proniosomal powder. Int J Pharm Pharm Sci, 2012; 4(11): 175-8.
11. Nasr M. In vitro and in vivo evaluation of proniosomes containing Celecoxib for oral administration. AAPS Pharm Sci Tech, 2010 Mar 1; 11(1): 85-9. DOI: 10.1208/s12249-009-9364-5.
12. Munish Ahuja and Kamal Saroha. Proniosomes Formulations Using Maltodextrin and Mannitol as Carriers. IJPCS, 2014; Apr-Jun 3(2): 547-551.

13. Naggar VF, El Gamal SS, Allam AN. Proniosomes as a stable carrier for oral Acyclovir: Formulation and physicochemical characterization. J Am Sci, 2012; 8: 417-28.
14. Solanki A, Parikh J, Parikh R. Preparation, characterization, optimization, and stability studies of Aceclofenac proniosomes. Iran J Pharm Res, 2008 Nov; 7(4): 237-246.
15. Sambhakar S, Singh B, Paliwal S, Mishra PR. Sorbitol based proniosomes to improve the permeability and stability of an oral Cephlosporin. Drug Delivery, 2012 Apr 1; 4(2): 236.