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Formulation and evaluation of meloxicam loded liposomal gel as vesicular carriers for enhanced skin delivery

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***Abstract*---**Background and objective: Applying liposomal gels in transdermal drug delivery system has evoked considerable interest because of their good activity for osteoarthritis. The aim of present study was to prepare and characterize liposomes of NSAIDS drug meloxicam, which may deliver these drugs to the target site more efficiently and also overcome the problem related with oral drug delivery of the drug. Methodology: In the present investigation efficiency of liposomes as a novel lipid for topical delivery of meloxicam has been evaluated. Liposomes were optimize by varying concentration of phospholipids cholesterol and ethanol. Liposomes formulation with soya lecithin, cholesterol and ethanol was optimized. Result: On characterization spherical, unilamellar vesicle with smooth surface were observed under Scanning electron microscopy and F4 formulation shows the best result. Conclusion: Suggested as liposomes as an efficient carriers for meloxicam topical drug delivery.

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***Keywords*---**Vesicle, meloxicam, in-vitro release, transmission electron microscopy, topical delivery.

Introduction

Topical drug delivery cause more and more attention over the past year, in this form the maximum drug concentration localized at the site of action. Paul Ehrlich in 1906 started the era of development for targeted delivery system where he envisaged a drug delivery mechanism where he directly target the drug to diseased cells, which he named as magic bullets.

A liposome is a spherical-shaped structure composed of one or more phospholipid bilayers surrounding an equal numbers of aqueous compartments. Liposome are able to encapsulate hydrophilic or lipophilic drugs. Drug encapsulated by liposomes achieve therapeutic level for long duration as drug must first be release from liposome before metabolism and excretion.

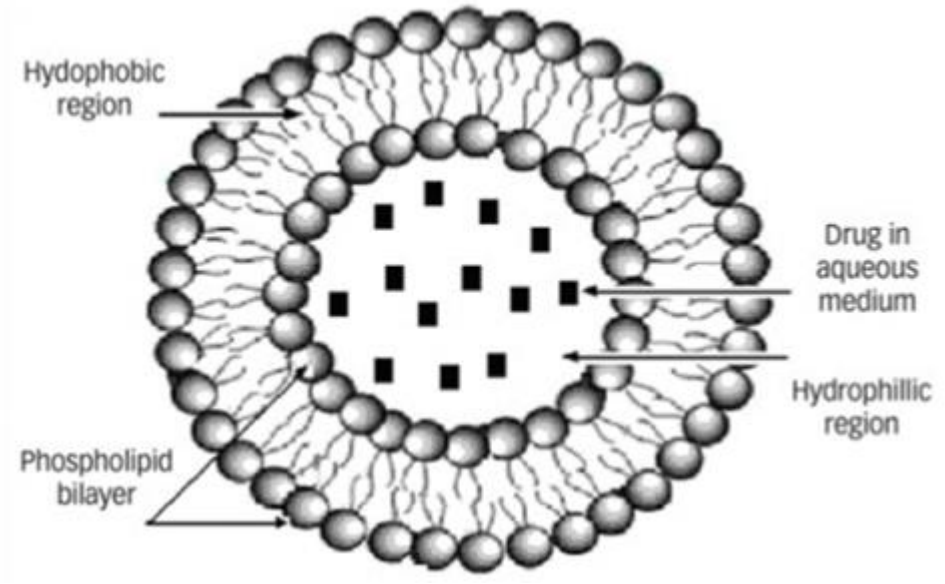


Fig: Structure of Liposome

Lipids are amphiphilic molecules with one water-loving (hydrophilic) and one water-hating (hydrophobic) side. When lipids come into contact with water, the hydrophobic portions of the molecule establish unfavourable interactions with the solvent, resulting in lipid self-assembly in the form of liposomes. By changing medication absorption, lowering metabolism, prolonging biological half-life, and reducing toxicity, liposomes have been utilised to increase the therapeutic index of new and old pharmaceutical features of the carrier, rather than the physico-chemical characteristics of the pharmacological molecule, are therefore used to govern drug distribution.

Liposomes can be made from natural or synthetic lipids, and liposome contents are not limited to lipids; new generation liposomes can also be made from polymers (sometimes referred to as polymersomes) Liposomes, which are made up of natural or synthetic lipids or polymers, are biocompatible and biodegradable, making them ideal for biomedical research.

The present investigation was to design the liposomal gel containing meloxicam using different concentration of phospholipids. This study shows that meloxicam (NSAIDS) is used as analgesic and anti-pyretic. In the present study, liposomal gel containing meloxicam was prepared by using ethanol injection method.

Material and Method

MLX were kindly provided by Yarrow chem products. Soy Lecithin was purchased from Central drug house, New Delhi. Cholesterol crystalline was purchased from SDFCL fine-chem limited, Ethanol was purchased from Central drug house, Carbopol 934 and Triethanolamine was also purchased from central drug house New Delhi.

Methods of preparation of meloxicam loaded liposomes

The liposomes were prepared by a modified ethanol infusion technique. The necessary dose of phospholipids and cholesterol was broken down into ethanol and the lipophilic drug was added in the natural stage. The next natural stage was infused through the needle siphon to the aqueous stage of 45 ± 2 ° C (the hydrophilic drug was added to the fluid phase) under an attractive mixture. Unconstrained liposome development occurred when the ethanol array contacted the aqueous phase. The suspension of liposomes was then kept stirred for 1 hour at room temperature for the hints of the soluble. The discharged drug was removed by ultracentrifugation of the suspended liposomes (Beckman Miami florida USA) at 6000 rpm for 1 hour. the pellets obtained were dispersed in a phosphate-based saline solution (PBS) and placed at + 4°c.

Method of Preparation of Liposomes Using Ethanol Injection Method

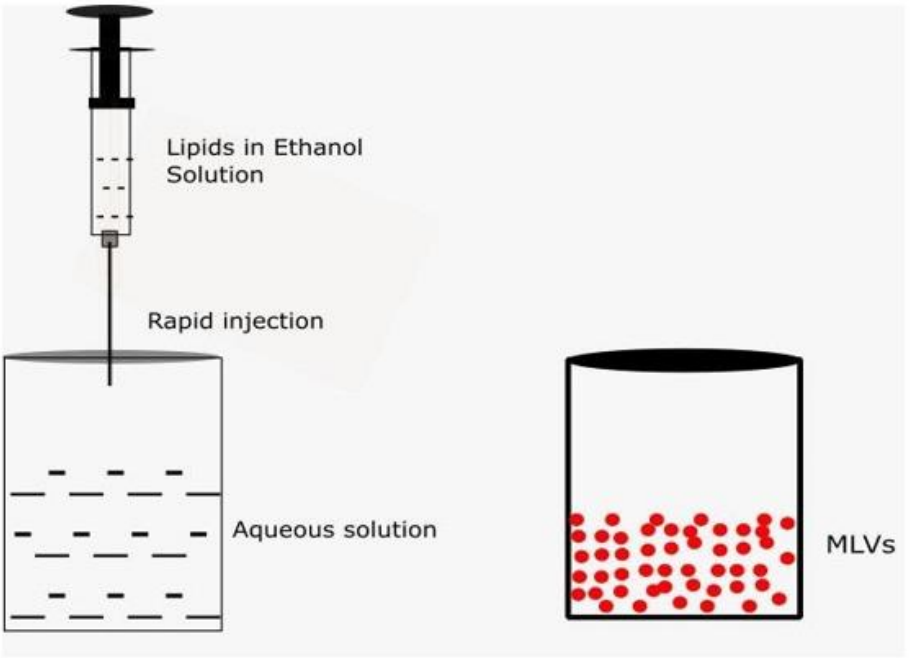


Fig: Method of Preparation of Liposomes Using Ethanol Injection Method

Table: Formulation design

Batch Code	Meloxicam (mg)	Phospholipids (mg/ml)	Cholesterol (mg/ml)	Org/aq. Phase ratio
F1	10	20	4	0.2
F2	10	20	4	0.2
F3	10	20	4	0.2
F4	10	40	4	0.2
F5	10	40	4	0.2
F6	10	40	4	0.2
F7	10	60	4	0.2
F8	10	60	4	0.2
F9	10	60	4	0.2

Preparation of Liposomal Gel

- The necessary amount of carbopol 934 powder was disseminated in hot distilled water (10 ml glycerol previously added) with a glass rod under continual stirring.
- Accurately weighed 0.02% and 0.01% of methyl paraben and propyl paraben respectively were also added into it.
- Take care not to create indispersible lumps, and left to hydrate for 24 hours at room temperature for swelling.

- Then, Triethanolamine (50 percent w/w) was used to neutralise the dispersion.
- Liposomes containing Meloxicam mixed into carbopol gel with a mechanical stirrer, at 25 rpm for 2 min.

Methodology

Organoleptic studies:
In this drug Appearance, Color and Order is checked**.**

Solubility studies

Semi quantitative determination of the solubility was made by adding solvent to glass tube containing accurately weighed amount of solute. The system is vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in terms of ratio of solute and solvent. The solubility study of meloxicam was performed in methanol, ethanol, acetone, hexane, ether, chloroform, propylene glycol, distilled water, phosphate buffer solution pH 5.5, 6.8, 7.4, separately by keeping the drug containing test tube on vortex mixture.

Determination of melting point

For determination of melting point USP method was followed. Small quantity of drug was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the observation of temperature was noted at which drug started to melt and the temperature when the entire drug gets melted was noted.

Determination of drug pH

The pH of meloxicam was determined using digital pH meter.

Determination of partition co-efficient

The known quantity of meloxicam was added into 20 ml of n-octanol and it was mixed with 20 ml of phosphate buffer pH 7.4 in a separating funnel. Then two phases were allowed to equilibrate at 37^0C for 2 hours with intermittent shaking. The concentration of drug in the aqueous phase and organic phase was determined by UV spectroscopic method at λmax 363 nm after necessary dilution. The apparent partition coefficient was calculated as the ratio of drug concentration in each phase by the following equation -

$$\mathbf{K\ p = C_{organic}\ /C_{aqueous}}$$

$C_{organic}$ is concentration of drug in organic phase $C_{aqueous}$ is concentration of drug in aqueous phase

Infrared spectroscopic analysis

The Fourier infrared spectrums of moisture free samples of meloxicam, soya lecithin, cholesterol, cholesterol were recorded in IR spectrophotometer. Infrared spectroscopy of different compounds was performed for identification of that particular compound. Spectroscopy was done using KBr pellets. Various peaks in FTIR spectrum were interpreted for identification of different group in the structure of meloxicam. FTIR Spectroscopy can also be used to investigate and predict any physicochemical interactions between different components. The scanning range varies from 4000– 400 cm-1 and the resolution was 1 cm-1.

Vesicle Size and Shape: Vesicle size and shape for each formulation was determined by optical microscope. 2 gm of each formulation was spread uniformly on glass slide and observed under optical microscope for vesicular size and shape.

Drug Release of Formulated Liposomes

This study was performed by dialysis membrane method. Into 50ml beaker dissolution medium (100ml) was placed. The beaker was placed on a magnetic stirrer at temp 37±5°. One end of the dialysis membrane was sealed in which liposome formulation was filled and sealed. The dialysis membrane containing sample was suspended in the medium from which 5ml of aliquots were withdrawn at specific interval of time which was immediately replaced with same quantity of fresh medium. The aliquots was measured for the amount of drug by using spectrophotometer.

Evaluation of Liposomal Gel

Physical evaluation of liposomal gel
The liposomal gel formulation was evaluated for organoleptic properties.

Measurement of pH of liposomal gel

1 gm of meloxicam liposomal gel was mixed in 100 ml distilled water with homogenizer. Then the electrode was immersed in the prepared gel solution and reading was recorded from digital pH meter in triplicate and average value was calculated.

Viscosity study

Viscosity measurement was done by Brookfield viscometer by selecting suitable spindle number and rpm. 50gm of preparation was kept in 50 ml of beaker which was set till spindle groove was dipped and rpm was set and dial reading was measured after three minutes. From the reading obtained, viscosity was calculated by using factor. The procedure was repeated three times and observations are recorded as mean.

Spread ability

It expressed the extent of area to which gel readily spreads on application to skin or affected area. It is expressed in term of time in seconds taken by two slide to slip off from gel placed in between the slides on applying load. Lesser the time required for separation of two slide, better the spreadability.
It is calculated by using the formula:

S = M.L/T

Where,
M = wt. tied to upper slide
L = length of glass slide
T = time taken to spread the slide

Percentage yield

The empty container in which the liposomal gel have to be stored was weighed. Then, container is weighed again after filling the formulation into it. The weight of the empty container was subtracted from the weight of the container containing the formulation to achieve the practical yield. Calculated by formula:

Percentage yield = Practical yield /Theoretical yield× 100

Homogeneity and grittiness

A small amount of liposomal gel were pressed between the thumb and fore finger or rubbed on the skin of back of the hand to check the consistency of the formulation. If there will be any coarse particle they will appear.

In-vitro release studies

This study was performed by dialysis membrane method. Into 50ml beaker dissolution medium (100ml) was placed. The beaker was placed on a magnetic stirrer at temp 37±5°. One end of the dialysis membrane was sealed in which liposome formulation was filled and sealed. The dialysis membrane containing sample was suspended in the medium from which 5ml of aliquots were withdrawn at specific interval of time which was immediately replaced with same quantity of fresh medium. The aliquots was measured for the amount of drug by using spectrophotometer.

Stability

Stability study of liposomal gel was calculated by keeping the gel into most satisfactory glass vial at 40c for a month, then placing the same vial at 25c for a month and then again at 40c for a month. After then liposomal gel was exposed to ambient room temperature therefore liquid exudates separating were noted. After the end of three month the physical characteristics were examined.

Result and Discussion

Preformulation studies, organoleptic properties

The meloxicam drug is of pastel yellow solid having unpleasant smell

S.NO.	Properties	Description
1	Appearance	Powder
2	Color	Pastel yellow
3	Odor	Unpleasant

Solubility study

Solubility studies are performed to determine the solubility of drug in different solvent

S.no	Quantity of drug	Solvent	Quantity of solvent	Inference
1	50mg	Water	5ml	insoluble
2	50mg	Diethyl ether	5ml	Soluble
3	50mg	Methanol	5ml	Slightly soluble
4	50mg	Polyethylene glycol	5ml	Highly soluble
5	50mg	Octane	5ml	Slightly soluble
6	50mg	Ethanol	5ml	Very slightly soluble

Melting point
Melting point of meloxicam was found to be 254c. It was measured 3 times and mean was noted.

Partition co-efficient
Partition co-efficient was measured three times and the mean were noted. Hence the partition co-efficient of meloxicam was found to be 0.1.

Concentration	Amount of drug in aqueous phase	Amount of drug in oil phase	Partition coefficient
n octanol : water	1.839	3.215	1.748
n octanol : PBS	0.986	2.051	2.8

FTIR analysis

FTIR spectroscopic analysis was carried out to characterize drug. The FTIR spectra obtained was compared with that given in pharmacopoeia for meloxicam. Diagnostic peaks and finger print regions were found identical. These characteristics peaks are useful in identification of drug. FTIR of soya lecithin and cholesterol was done to identify the compatibility of components in the formulation so that no interaction occur between the components.

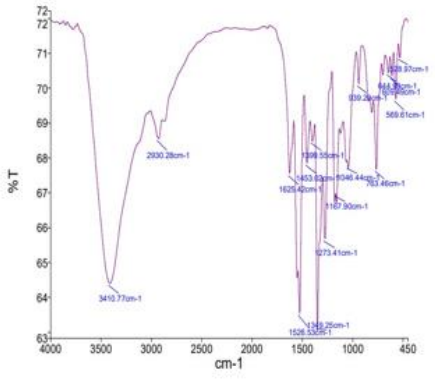


Fig: FTIR OF MELOXICAM

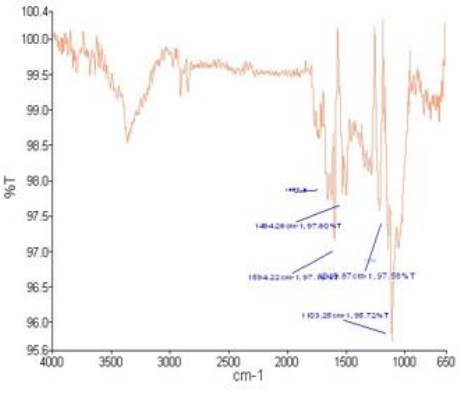


Fig : FTIR OF SOYALECITHIN

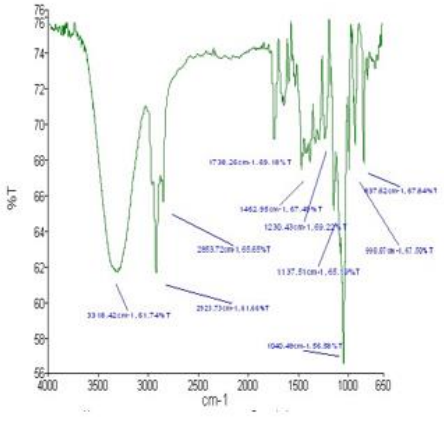


Fig: FTIR OF CHOLESTEROL

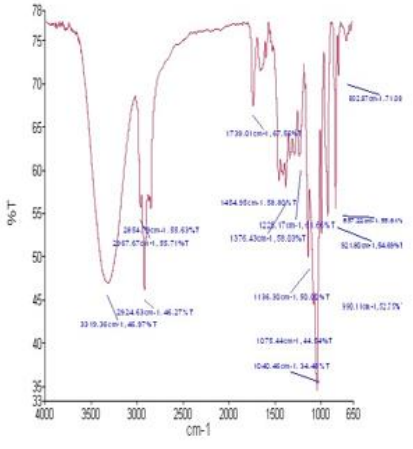


Fig:FTIR OF PROPYLENE GLYCOL

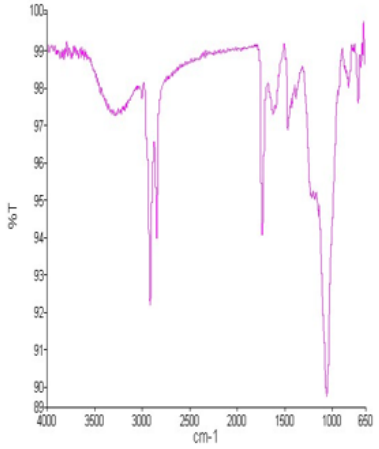


Fig: FTIR OF MELOXICAM + SOYALECITHIN

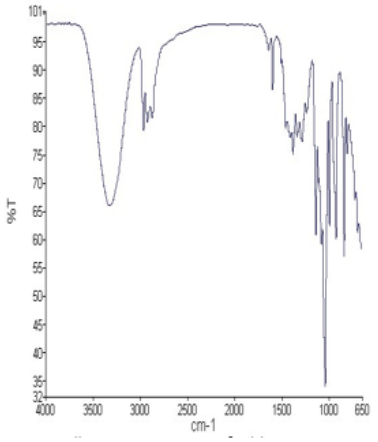


Fig: FTIR OF MELOXICAM+PROPYLENE GCL

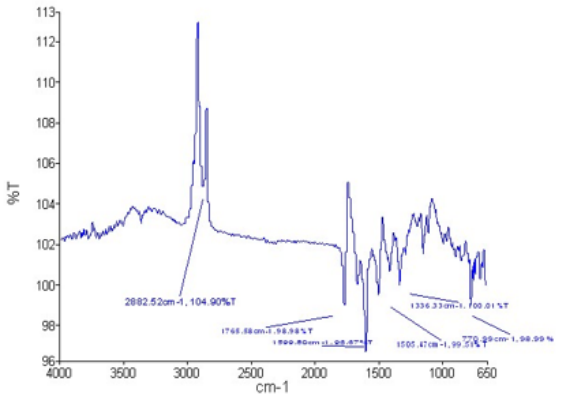


Fig: FTIR OF MELOXICAM +CHOLESTEROL

Evaluation of Liposomes

Percentage of intarpation of the medicinal product

5 ml of phospholipid formulation were withdrawn and transferred to a 100 ml volumetric flask containing 25 ml of mobile phase which was then sonicated by ultrasonic bath for a few minutes and filtered through a 0.5 µm membrane filter. The mobile phase was used to dilute the filtrate and an appropriate dilution was made. The absorbance was recorded by the Shimadzu 1700 UVVIS spectrophotometer at 363 nm respectively and the amount of meloxicam was determined. The drug entrapment rate was calculated using the following formula

$$\%EE \quad \frac{amount\ of\ drug\ entrapped\ in\ liposomes}{total\ drug\ added}$$

The main % of drug entrapment was measured after performing the experiment in triplicate.

Table: Percentage drug entrapment of meloxicam loaded liposomes

Formulation	%Drug Entrapment
F1	35.29
F2	28.58
F3	38.57
F4	46.71
F5	41.43
F6	56.14
F7	61.29
F8	63.86
F9	72.87

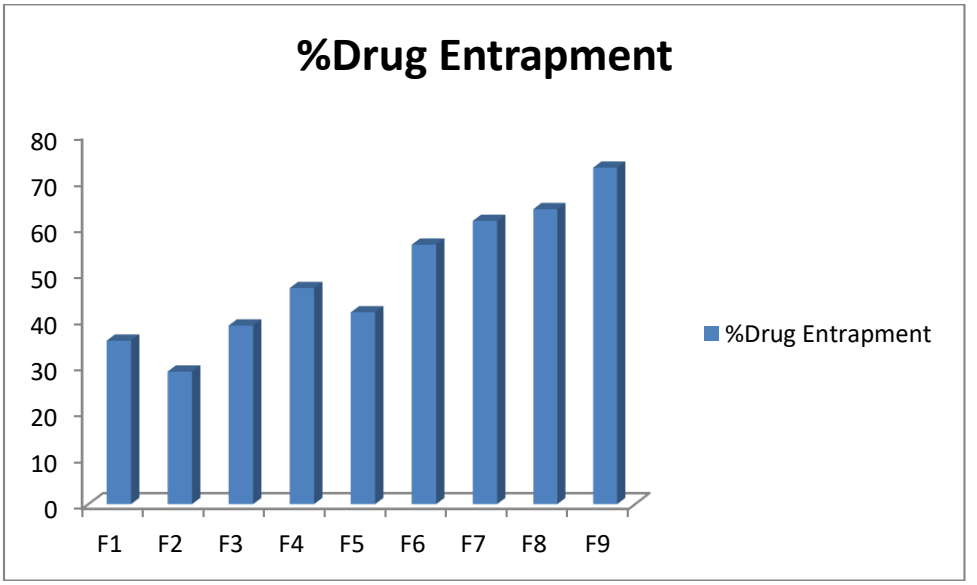


Fig: Graph Percentage drug entrapment of meloxicam loaded liposomes

SEM Analysis

SEM imaging was done to study the morphology of the optimized batch of Meloxicam. *SEM* Scanning electron micrograph (SEM) of the optimize batch was done.

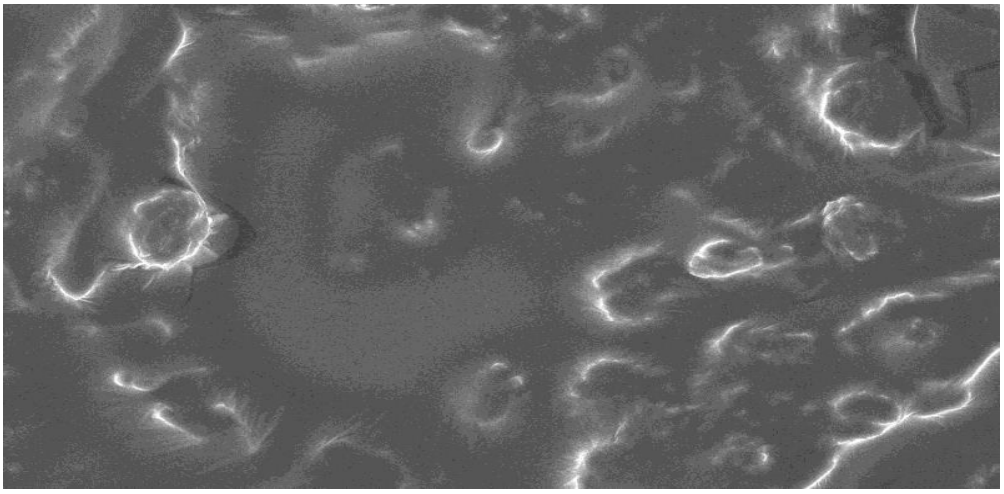


Fig: SEM Image of optimized batch of Meloxicam

IN VITRO drug release meloxicam loaded Liposomes

The decay profile of details F1 to F6 was not very high due to drug discharge (30.6-67.42%) at 2 hours. The F9 drug discharge shows an optimal needs control discharge profile in all definitions. The side effect of F9 shows the arrival of 32.48% of the drug during the 2 hours of introduction.While 61.1% of the drug was dispensed within the first 4 hours and the rest of the drug was dispensed within the last 4 hours. Controlled drug dump was shown by F7, but shows the least extent of drug dump. Therefore, the F7 tuft was not considered for further examination.

Table– In vitro release profile of Meloxicam loaded liposomes

Time (H)	CUMULATIVE % DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	4.34	4.40	3.56	4.00	5.24	4.80	3.46	3.09	3.45
1	9.36	10.80	8.60	8.75	10.21	7.80	6.00	5.64	6.75
1.5	12.03	12.81	10.67	12.50	15.45	12.80	9.64	9.09	8.63
2	18.05	19.61	15.71	17.26	19.59	19.80	13.46	14.00	12.71
2.5	23.73	27.21	20.15	24.76	26.49	26.40	18.00	18.37	15.69
3	30.08	39.62	26.08	35.76	38.08	34.60	23.28	22.01	20.71
3.5	36.76	44.02	37.64	44.01	41.94	42.20	34.37	25.28	26.52
4	43.78	52.82	45.35	50.02	46.63	52.20	39.10	27.46	34.67
5	56.14	60.42	58.98	62.77	58.22	62.00	48.38	36.56	46.91
6	66.83	71.63	69.95	72.27	64.57	70.40	53.29	46.56	56.64
7	71.51	78.43	77.36	80.03	76.98	77.60	56.74	54.92	65.43
8	86.88	84.03	83.88	87.78	82.50	80.00	59.65	61.65	72.49

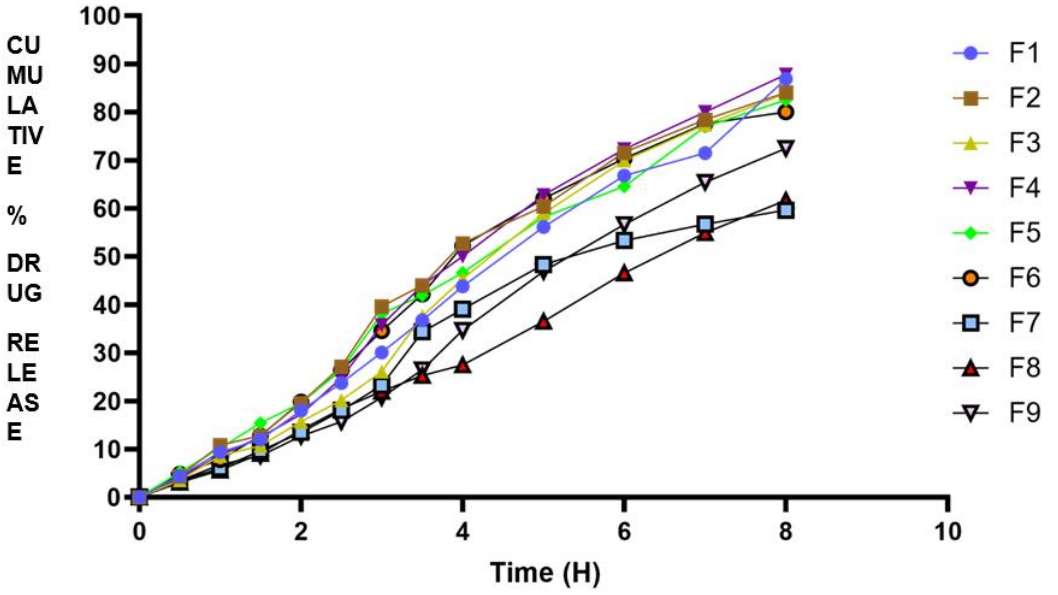


Fig.: Release profile of Meloxicam loaded liposomes

Physical evaluation of liposomal gel
The liposomal gel formulation of meloxicam was evaluated
Organoleptic characteristics color = pale yellow to colorless
Odor = characteristic
Appearance = Smooth.
Determination of pH of gel base and liposomal gel:
The pH was measured three times and mean was noted. The Ph of meloxicam gel was found to be 7.38.

Viscosity
Viscosity of formulation determined with Brookfield viscometer. viscosity found 47889±1.13 centipoise Viscosity play important role in stability and during applying.

Spreadability
24 hr old gels was placed between two horizontal plates of 20 cm^2, of which the upper one weighted 46.36 gm and 200gm weight was placed over it at ambient temperature. A circle of 5 mm in diameter was made and the diameter of gel was measured after 5 minutes .

Homogeneity and grittiness
Liposomal gel was found to be homogenous and no grittiness was observed.

Presence of different functional group:
To identify the presence of organic functional groups in the prepared Proniosomal formulations FTIR study was performed. We were seen there is no any type of interaction in the drug and excipients.

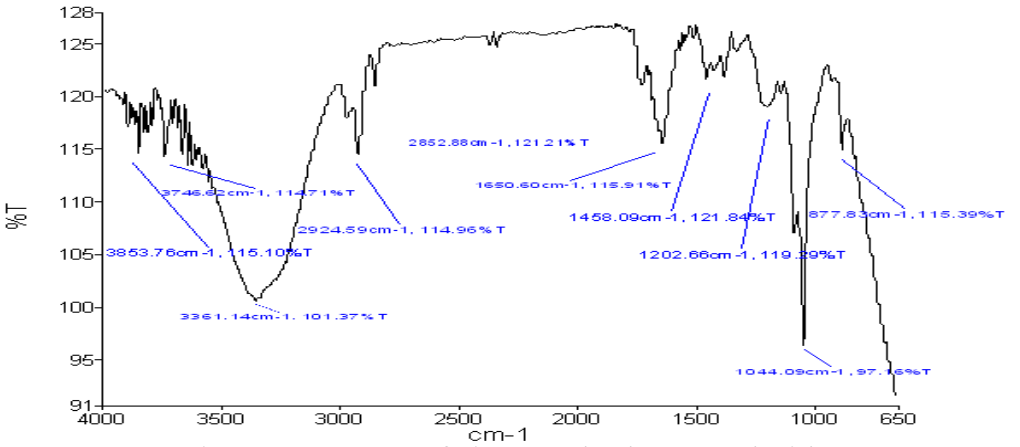


Fig - FTIR spectra of Liposomal gel prepared with MLX

Skin irritation test

The skin irritation test study of liposomal gel revealed no irritation.

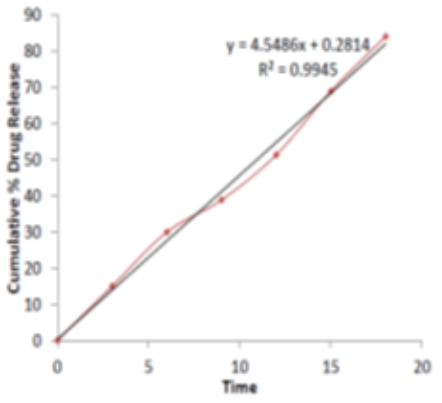
Physical appearance

It was observed that optimized gel was kept for 3 months at 40c, 25c, 40c temperature conditions showed no change in their physical appearance.

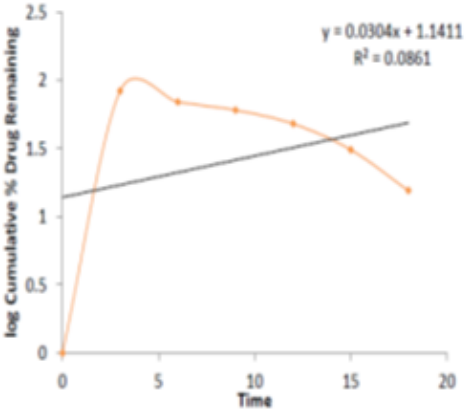
Phase separation

No phase separation was observed in the optimized liposomal gel.

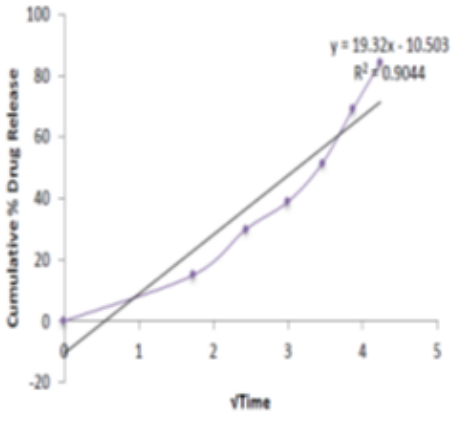
In-vitro drug release of meloxicam loaded liposomal gel: The drug release was checked by using Franze diffusion cell by using cellophane membrane.



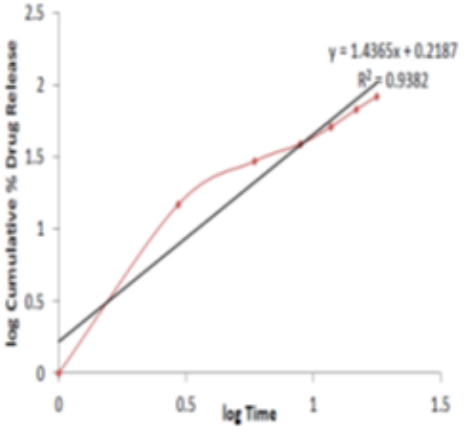
Graph: Cumulative % Drug Release vs Time (Zero Order)



Graph: log Cumulative % Drug Remaing vs Time (First Order)



Graph: Cumulative % Drug Release vs √Time (Higuchi Order)



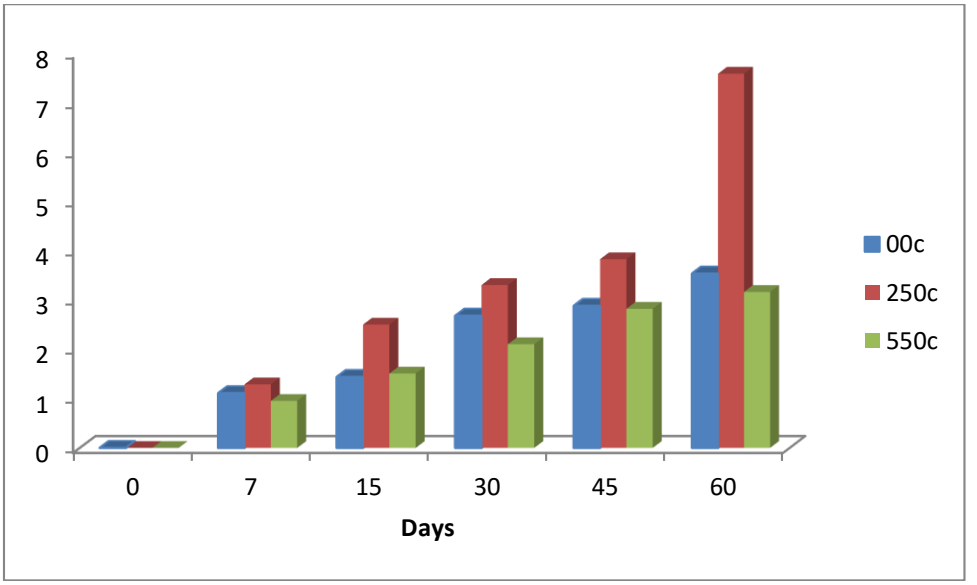
Graph: log Cumulative % Drug Release vs log Time (Peppas Order)

Stability studies

Stability studies performed at 0c and 25c for 2 months. The ability of vesicles to retain the drug (Drug Retention Behaviour) was assessed by keeping the formulated liposomal gel at two different temperature conditions on the basis characterization vesicle size and drug content.

Table: Stability parameters of all formulations

Time in Days	0^0c	25^0c	55^0c
	Percentage Drug leakage	Percentage Drug leakage	Percentage Drug leakage
0	-	-	-
7	1.12	1.30	.96
15	1.45	2.52	1.52
30	2.70	3.32	2.12
45	2.90	3.84	2.84
60	3.55	7.58	3.18



Graph: Stability parameters of all formulations

Conclusion

Liposomes gel of meloxicam have been formulated of medications to improve therapeutics, minimise toxicity, and increase efficacy in the treatment of diseases.Liposomes are now being used more in dermatology, vaccine adjuvant, infectious disease, immunology, ocular problems, and tumour therapy. Targeting liposomes has resulted in drug buildup at illness sites and reduced distribution to sensitive tissues, thanks to a number of discoveries.As a new generation of liposomes, stealth liposomes have been used in a variety of therapeutic applications. Liposomes with improved drug delivery to disease sites due to their capacity to stay in circulation for lengthy periods of time are increasingly gaining clinical acceptability. Only time will tell whether of the aforementioned applications and hypotheses will be effective. However, we can claim that liposomes have firmly secured their place in modern delivery systems based on pharmaceutical uses and available items. Meloxicam is used for the treatment of osteoarthritis, in addition to its analgesic and antipyretic effect.

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