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FORMULATION AND EVALUATION OF MELOXICAM-LOADED TRANSFERSOME GEL AS TRANSDERMAL DRUG DELIVERY CARRIERS

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Abstract:

Transfersomes (TFS) are the promising carriers for transdermal delivery of various low and high molecular weight drugs, owing to their self-regulating and self-optimizing nature. Herein, we report synthesis and characterization of TFS loaded with meloxicam (MLX), a Nonsteroidal anti-inflammatory drug (NSAIDs) for transdermal delivery. The different formulations of TFS containing varying amounts of lecithin, Span 80, and Tween 80 were successfully prepared by thin-film hydration method. FTIR pre-formulation investigations conformed that there was no contact among the medication and excipients, according to the FTIR spectra. Thin film hydration was used to create the transfersome formulations, which were then added to the 1.5% Carbopol gel. The Formulation F6 has a greater entrapment efficiency and maximum drug release since it contains Lecithin: Span-80 in a ratio of 89.84 (%w/w). A greater correlation with Higuchi's equation was discovered to fit the kinetic analysis of the transfersome gel formulation than with the zero order and first order. This claims that diffusion process was primarily responsible for the drug's release from the lipid bilayer. According to stability studies for improved transfersome gel formulations, manufactured transfersomes are stable at room temperature. Finally, it can be inferred from the findings of the current study that transfersome gel enhances the transdermal distribution of the medication Meloxicam, prolongs the release, and improves site specificity. With the use of transfersomes, a number of medications that are difficult to administer through other methods can now be delivered safely and effectively transdermally.

Keywords: *Transfersomes, NSAID, Meloxicam, lecithin, Span 80, Tween 80, Carbopol, gel.*

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INTRODUCTION:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs due to their analgesic, antipyretic, and anti-inflammatory effects. A range of inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis require the use of NSAIDs for longer times [1]. NSAIDs exert their anti-inflammatory action by inhibiting the cyclooxygenase enzymes with a consequent reduction in the prostaglandin level [2]. These prostaglandins are crucial to prevent the stomach lining from the corrosive action of the stomach acid. Thus, stomach disturbance is the major adverse effect associated with continuous oral therapy of the NSAIDs. Other systemic adverse effects include platelet aggregation inhibition, anemia, kidney damage, and cardiac degradation [3]. Therefore, the transdermal delivery of NSAIDs for the local action is a desirable approach for the optimal management of inflammatory conditions of skin as an alternative parenteral or oral therapy. Given this, various conventional dosage forms have been developed like transdermal gels, ointments, and creams for their longer contact time with the skin surface and releasing the therapeutic moiety to be absorbed via the skin [4]. However, the skin is not freely permeable to all drugs, and these dosage forms are suitable only for those drugs that can easily permeate the stratum corneum (SC) of the skin. Several formulation strategies have been adopted to enhance the delivery of limited permeable drugs against the SC layer including the incorporation of a chemical permeation enhancer, iontophoresis, electrophoresis, and microneedle patches [5]. Recently, topical delivery of therapeutic moities incorporated into lipid-based carriers like liposomes, niosomes, ethosomes, and transfersomes have attained huge attention [6].

The vesicular carrier system can entrap drug molecules by acting as a drug carrier and increase the permeation of drugs into the stratum corneum. As far as topical vesicular systems are concerned, unfortunately, the first-generation nanovesicular systems including liposomes and niosomes were accompanied with drawbacks, particularly weak stratum corneum (SC) penetration because of their inflexible nature [7]. Among all other vesicular carriers, ultradeformable vesicular drug carrier system “Transfersomes”(TFS) have been considered as surrogate vehicles for transdermal drug delivery of a wide range of hydrophilic as well as hydrophobic drug molecules. TFS are complex aggregates of highly deformable and stress-responsive vesicles. TFS are the first-generation deformable vesicles developed for the first time by Cevc and Blume [8]. TFS could be loaded with a variety of low molecular weight drugs as well as with high molecular weight drugs [9]. In this study, lecithin was used as main component of TFS due to its inherent characteristics such as solubilization of the substances with different physiochemical properties, biocompatibility, thermodynamic stability, thermoreversible nature, and resistance to microbial contamination [9]. As the lecithin itself provides skin protection against UV induced skin aging, it shows additional effects along with incorporated bioactive agents against skin aging Gels are considered promising vehicles to retain drugs or nanoparticles at the site of application. Gels also increase the residence time of the drug due to their mucoadhesive character [10]. The incorporation of TFS in carbopol-940 gel matrix in current study would have potential to increase the residence time at the inflamed body site, enabling the TFS to penetrate efficiently through the skin for a longer duration.

Therefore, this research is aimed at developing TFS loaded with meloxicam (MLX) and subsequent incorporation into carbopol-940 gel for enhanced skin permeation, which may have the ability to suppress adverse effects associated with peroral therapy and treat severe pain and inflammatory conditions effectively [11]. TFS were characterized for entrapment efficiency (EE), vesicle size, polydispersity index (PDI), zeta potential, release profiles, and *in vitro* permeation studies. Kinetic models were applied to release data of TFS to find out best fit model and mechanism of release. TF-based gels (TF-Gs) were also evaluated for spreadibility, viscosity, homogeneity, drug release.

MATERIALS AND METHODS:

Materials

Meloxicam was obtained from Hetero drugs Ltd., Hyderabad, India. Lecithin, Tween 80, Span 80was obtained from Merck specialties pvt. limited (Mumbai)

Methods

Drug and polymer compatibility studies by using FTIR

To make potassium bromide pellets with a KBr press, the powder sample was mashed in a mortar with 100 times the quantity of potassium bromide and compressed at a pressure of around 8t/in2. The wavelength range of the spectra was 35000 to 500cm-1 [12].

Preparation of Transfersomes Containing Meloxicam:

Meloxicam, soy lecithin, and several surfactants were used to prepare 12 different Transfersome formulations utilising the thin film hydration method. The dosage remains the same (20 mg) throughout all formulations. Different surfactants were used in various ratios to prepare various formulations. In 5ml of an organic solvent (methanol: chloroform: 1:1), lecithin, surfactants, and the medication are dissolved. Evaporation is then used to get rid of the organic solvent. Rotating the deposited lipid film for an hour at room temperature at 60 revolutions per minute hydrates it with the phosphate buffer (pH 7.4). At room temperature, the resultant vesicles swell for two hours [13]. The multilamellar lipid vesicles are subsequently sonicated for 30 minutes at 40°C using a probe sonicator (Heldolph vcx750).

Table 1: Formulation table shows for preparation of transfersomes

FORMULATION No. (mg)	Drug Meloxicam	Lecithin	Tween 80	Span 80	Span 60	Span 40
F1	20.0	90.0	10.0	-	-	-
F2	20.0	85.0	15.0	-	-	-
F3	20.0	80.0	20.0	-	-	-
F4	20.0	90.0	-	10.0	-	-
F5	20.0	85.0	-	15.0	-	-
F6	20.0	80.0	-	20.0	-	-
F7	20.0	90.0	-	-	10.0	-
F8	20.0	85.0	-	-	15.0	-
F9	20.0	80.0	-	-	20.0	-
F10	20.0	90.0	-	-	-	10.0
F11	20.0	85.0	-	-	-	15.0
F12	20.0	80.0	-	-	-	20.0

Each formulation had 2.5ml of methanol and 2.5ml of chloroform added separately

Preparation of topical transfersome gel:

The aqueous dispersion of transfersomes was used to create the topical gel. To make transfersome gel, a gel polymer like carbopol 934 was used. Taking care to prevent the formation of insoluble lumps, 1.5% of carbopol-934(fg2) powder was dissolved in rapidly agitated (stirred by magnetic stirrer Remi 5MLH) distilled water and left to hydrate for 24 hours [14]. Propylene glycol was added in the final 1-2 ml. Using a pH metre (Lab India Sab 5000), the dispersion was neutralised with triethanolamine to adjust the pH to 7.4.

Table 2: Formulation of Gel

INGREDIENTS	FG1	FG2	FG3
Carbopol 934(mg)	100	150	200
Water(ml)	10	10	10

FG1 was discarded due to low consistency of gel.
FG3 was discarded due to high consistency of gel.

OPTIMIZATION OF FORMULATION:

The preparation and qualities of the transfersomes may be impacted by a number of procedural variables. As a result, the preparation process was improved and verified. The impact of lecithin is just one of many process variables that come into play during the creation of transfersomes containing meloxicam. The optimisation of the surfactant ratio (90:10,85:15,80:20) and the effects of different surfactants (Span80, Tween80) was carried out by choosing the in vitro drug release as the optimising parameter [15]. The other variables were held constant while creating a specific system.

CHARACTERIZATION OF TRANSFERSOMES:

Vesicle shape and type:

By using an optical microscope, transfersome vesicles can be seen. Using an optical microscope, the form and surface characteristics of the transfersome vesicle were projected [16].

Vesicle size, size distribution and zeta potential:

Zetasizer was used to determine the average diameter, size distribution profile, and zeta potential analysis of the vesicles

pH:

At room temperature, the pH of topical transfersome gels was determined using a digital pH meter.

Determination of entrapment efficiency percentage:

By using centrifugation, the quantity of Meloxicam trapped in transfersome gel was calculated. 10ml of phosphate buffer (pH 7.4) was used to dilute 1gm of

Transfersome gel. For 20 minutes, this suspension was sonicated in a bath sonicator. Later, a centrifuge tube containing this solution was filled, and it was centrifuged at 14000 rpm for 30 minutes [17]. Before measuring absorbance using a UV spectrophotometer at 380 nm, 0.5 ml of supernatant was taken out and

$$\% \text{ Entrapment} = \frac{\text{Whole drug} - \text{Diffused drug}}{\text{Total drug}} \times 100$$

% Drug content:

Vesicles were lysed using 25 ml of methanol and 1 g of the transfersome gel formulation using a sonicator for 15 minutes [citizen, India]. Later, a centrifuge tube containing this solution was filled, and it was centrifuged at 14000 rpm for 30 minutes [18]. Methanol was used to dilute the clear solution to 100 ml. Using a saline phosphate buffer with a pH of 7.4, 10 ml of the solution was then diluted to 100 ml. Meloxicam's drug content was determined after aliquots were taken out using a UV spectrophotometer set to 380nm.

% Drug Content = Amount of Medicine got after centrifugation/ Amount of medicine taken X 100

In-vitro drug release studies:

This study used a modified Franz diffusion cell with an effective diffusion area of 2 cm^2. Egg membrane was put horizontally atop the receptor compartment of a Franz diffusion cell to conduct an in-vitro drug release research. The donor compartment was exposed to a 30ml-volume receptor compartment with an effective permeation area of 2cm2. The receptor compartment's 30ml of phosphate buffered saline (pH 7.4) was stirred using a magnetic stir bar rotating at a speed of 100 revolutions per minute. The diffusion cell was covered with a 5mg drug-equivalent formulation of Transfersome gel. At the suitable intervals, 2.5 ml aliquots of the receptor medium were removed to preserve sink conditions [19], and they were immediately substituted with an equivalent volume of freshly made phosphate buffers (pH 7.4). The samples were spectrophotometrically examined at a maximum wavelength of 380 nm.

In-vitro release kinetics

Table 3: Kinetic equations of different models

S. No.	Model	Equation
1	Zero order	$Q_t = Q_0 + K_0 t$
2	First order	$L_n Q = K t$
3	Hixson crowell	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$
4	Higuchi	$Q = K_{HG} t^{½}$
5	Korsemeyer-peppas	$M_t / M_\alpha = K_{kp} t^n$

Stability Studies of transfersomes:

The three batches of the same formulation were stored in sealed glass ampoules (one each) at room temperature (25±2°C) for at least 30 days after measuring the first % entrapment of the medication in the optimised formulation [20]. After 30 days, the formulations' drug content and percentage of drug entrapment were calculated in order to establish how much of the drug had seeped out. The amount of drug lost was determined using a 100% initial drug entrapment rate.

RESULTS AND DISCUSSION:

Drug excipient compatibility study:

In order to conduct compatibility investigations, an FTIR spectrophotometer was used. We looked at the infrared spectra of both pure Meloxicam and a physical mixing of the drug and various excipients.

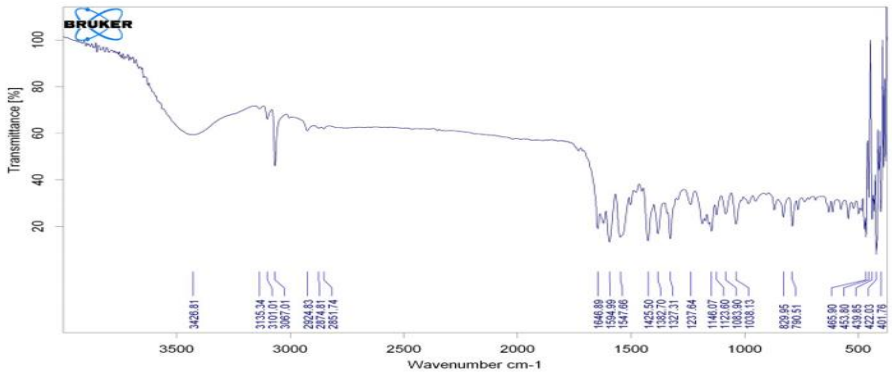

Fig 1: FTIR Spectra of Meloxicam pure drug

Table 4: FTIR Data interpretation

S.No	Wave number in formulation (cm^{-1})		Characteristic wave number range (cm^{-1})	Bond nature and bond attributed
	Pure drug	Optimized formulation		
1	829	830	900 - 675	C-H Stretching Aromatic
2	1238	1237	1250 - 1020	C-N Stretch Aliphatic amines
3	1327	1325	1335 - 1250	C–N Stretch Aromatic amine
4	1425	1466	1400 - 1500	C-C (Stretching) aromatic
5	1594	1595	1540 - 1850	-C=O Stretching
6	2924	2920	3000 - 2850	C-H Stretch Alkanes
7	3067	3067	3000 - 3100	=C-H Stretch

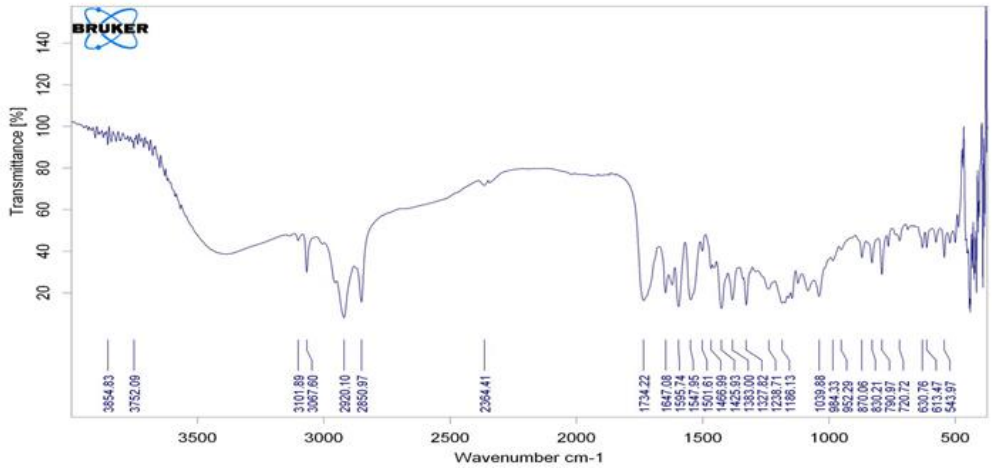

Fig 2: FTIR Spectra of Optimized formulation

CHARACTERIZATION OF TRANSFERSOMES:

Vesicle shape and type:

Most of the transfersomes identified to contain meloxicam were found to be spherical in shape.

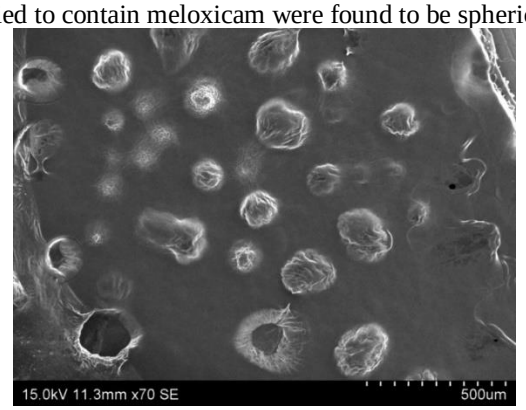

Fig 3: Photomicrograph of Meloxicam loaded transfersome (F6) at 10X

Vesicle size, size distribution and surface charge (zeta potential):
Zeta potential was found to be -14.3 mV and the mean vesicle diameter to be 195.3 nm, PDI of -14.3.

Entrapment efficiency:
Deformable vesicle formulations' % entrapment efficiency was observed to range from 82.84 ±0.049 to 89.85± 1.359. The f6 formulation's entrapment efficiency was high (maximum 89.84763 for f6). Because of the rise in the ratio of vesicle lipid volume to encapsulated aqueous volume, formulation f6 was determined to have the highest percentage of Meloxicam entrapment. When the lipid to surfactant molar ratio was lowered from 90:10 to 80:20, the effectiveness of drug entrapment reduced. The efficiency improved with rising lipid concentration and decreased with increasing surfactant concentration.

Table 5: % Drug entrapped and % Drug content in transfersomes

Surfactants	Formulations	Entrapment efficiency (%)	Drug content (%)
Tween 80	f1	87.22 ± 1.08	84.1 ± 0.77
Tween 80	f2	84.04 ± 1.85	86.2 ± 0.65
Tween 80	f3	83.71 ± 1.65	83.4 ± 0.9
Span 80	f4	86.24 ± 0.85	84.1 ± 0.87
Span 80	f5	87.53 ± 1.02	85.7 ± 0.86
Span 80	f6	89.84 ± 1.35	91.8 ± 1.09
Span 60	f7	84.25 ± 0.85	84.5 ± 1.20
Span60	f8	86.71 ± 0.88	85.3 ± 0.55
Span 60	f9	84.52 ± 1.08	85.6 ± 0.78
Span40	f10	87.92 ± 1.07	83.2 ± 1.15
Span 40	f11	84.76 ± 1.38	84.6 ± 0.96
Span 40	f12	82.84 ± 0.49	84.9 ± 0.66

pH
All topical transfersomal gels were found to have pH values between 7.4 and 7.4-0.08.

***In-vitro* drug release study:**
All twelve formulations' results from the diffusion studies have been compared. In comparison to other formulations, formulation f6 (lecithin: span80 in the ratio 80:20) was found to have a higher rate of drug release. This disintegration profile result showed a minimal first burst release. This is most likely brought on by a medication that was absorbed onto the surface of the transfersome or that precipitated from the topmost lipid layer. The subsequent stage's prolonged release can be due to the drug's delayed diffusion out of the lipid vesicle.

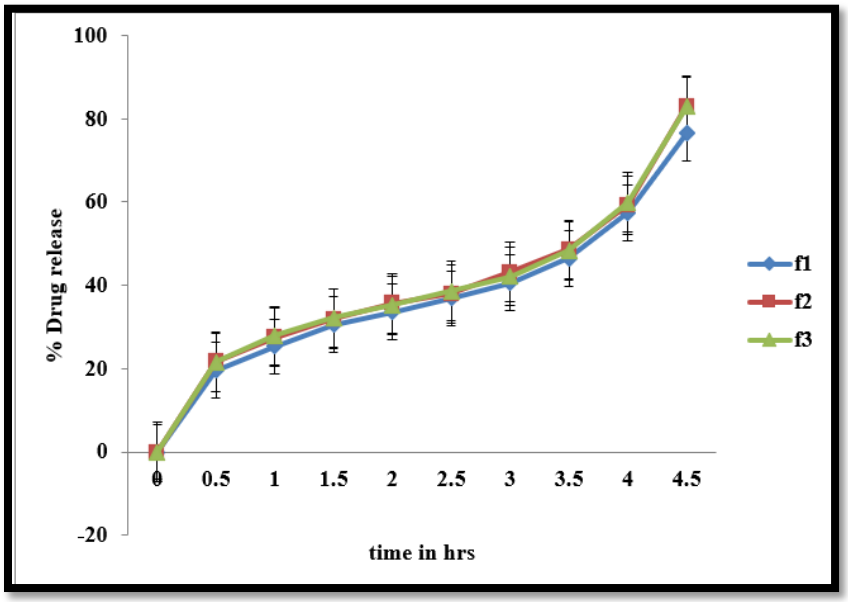

Fig 4 : In-vitro drug release study of f1 , f2 , f3 (Tween-80)

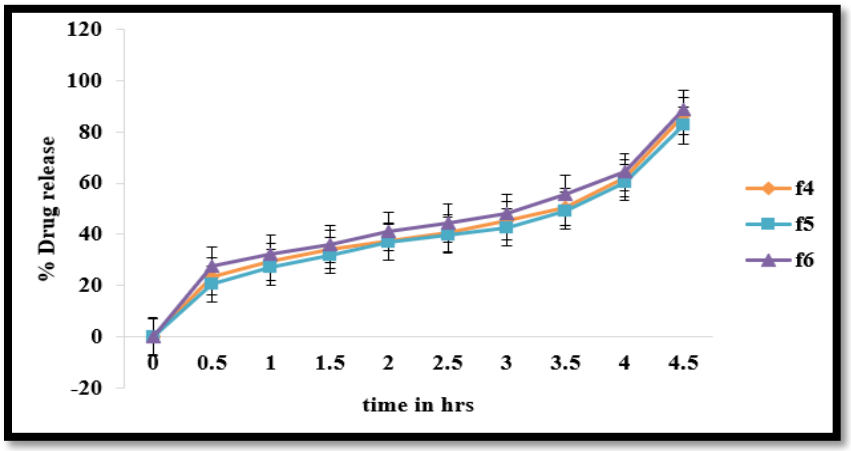

Fig 5: In-vitro drug release of f4 , f5 , f6 (Span-80)

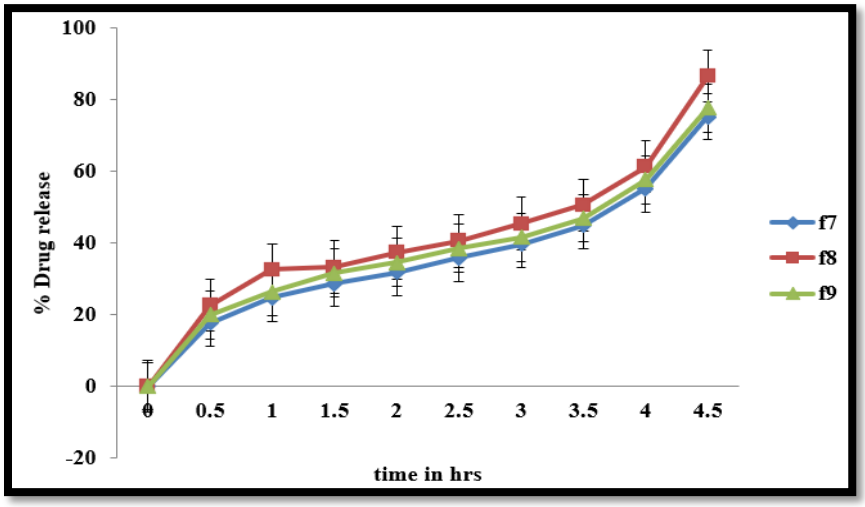

Fig 6: In-vitro drug release study of f7 , f8 , f9 (Span-60)

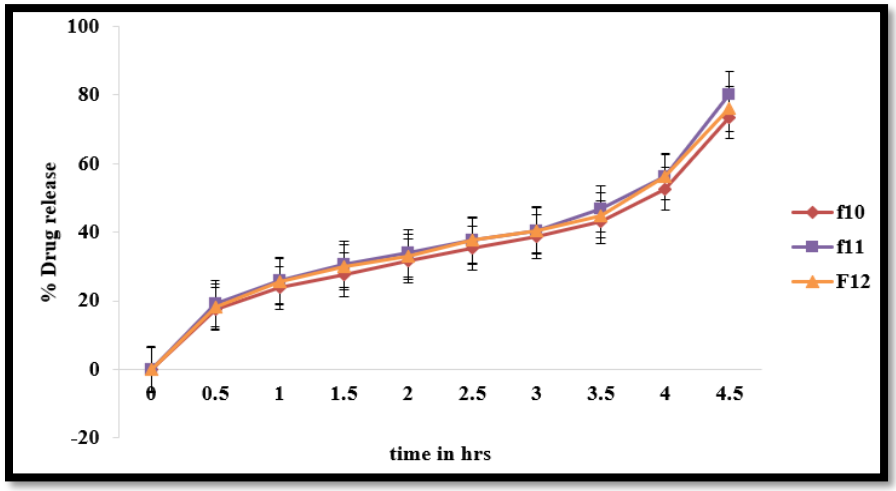

Fig 7: In-vitro drug release study of f10 , f11 , f12 (Span-40)

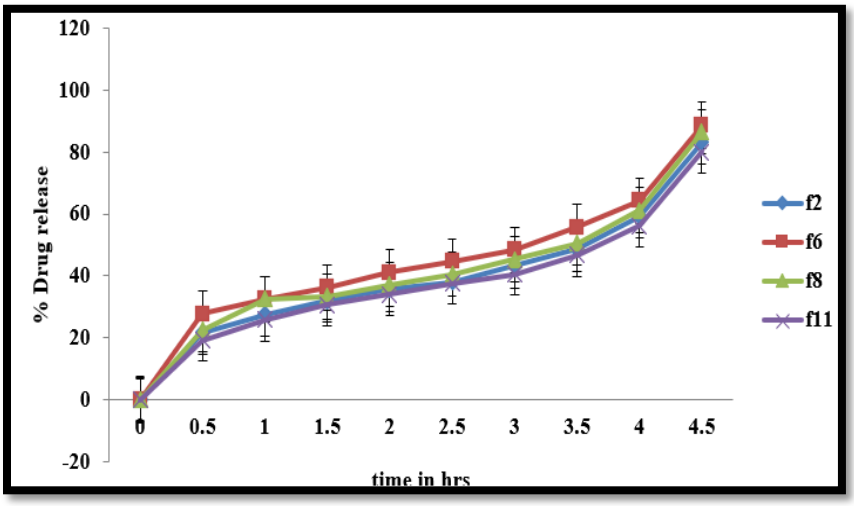

Fig 8: In-vitro drug release study of f2 , f6 , f8 , f11

Kinetic analysis of diffusion data:

The sort of release mechanism used was investigated using the drug release data. For several kinetic equations (zero order, first order, peppas, and Higuchi equation), release kinetic studies of all formulations (F1 to F12) were investigated. For all of the formulations, the Higuchi's equation provided the best match with a greater correlation (r2 > 0.893), indicating that the release of Meloxicam from the lipid bilayer vesicles was caused by diffusion. By entering the release data values in a Microsoft Office Excel Worksheet, the release kinetic research was once more confirmed, and it was discovered that all formulations adhere to the Higuchi model. Therefore, we may conclude that the diffusion mechanism was primarily responsible for Meloxicam's release from the lipid bilayer system.

Table 6: Kinetic assessment of diffution data of topical transfersome gel formulations

Formulations	Zero order (r^2)	First order (r^2)	Peppas (r^2)	Higuchi (r^2)	"n"value
f1	0.880	0.714	0.824	0.861	0.314
f2	0.843	0.759	0.862	0.884	0.342
f3	0.845	0.821	0.860	0.899	0.453
f4	0.842	0.709	0.845	0.873	0.326
f5	0.799	0.730	0.816	0.869	0.316
f6	0.894	0.778	0.774	0.893	0.562
f7	0.852	0.811	0.875	0.876	0.436
f8	0.858	0.765	0.848	0.884	0.348
f9	0.865	0.840	0.877	0.905	0.463
f10	0.852	0.830	0.855	0.907	0.452
f11	0.881	0.772	0.849	0.877	0.342
f12	0.874	0.842	0.870	0.865	0.412

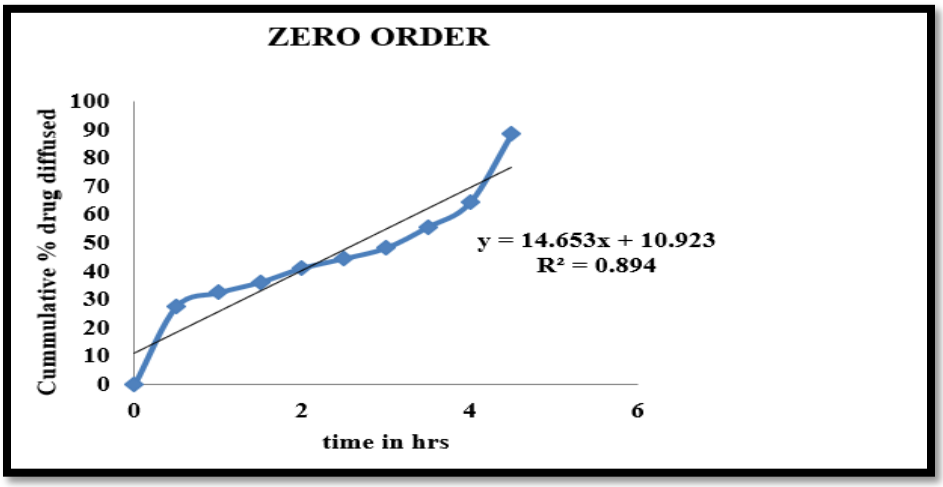

Fig 9: Zero Order release kinetics of formulation F6

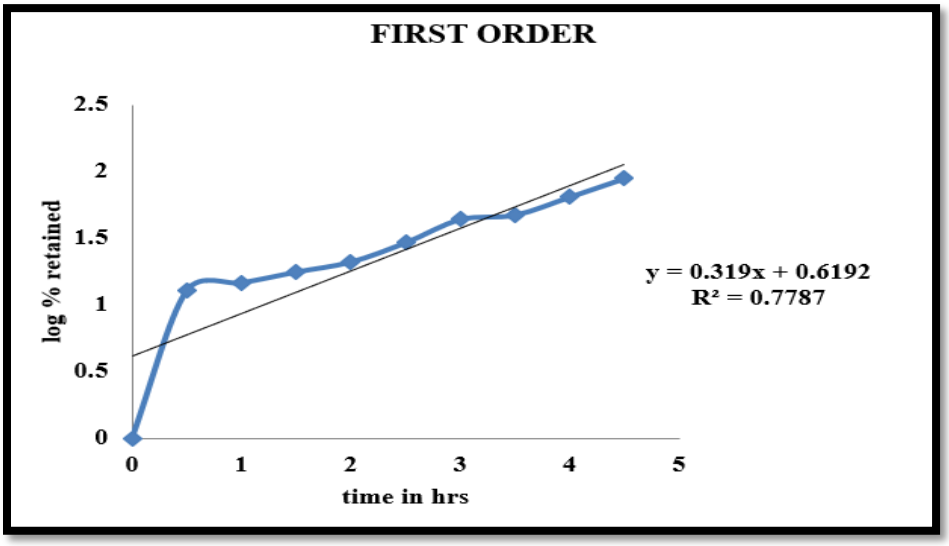

Fig 10: First Order release kinetics of formulation F6

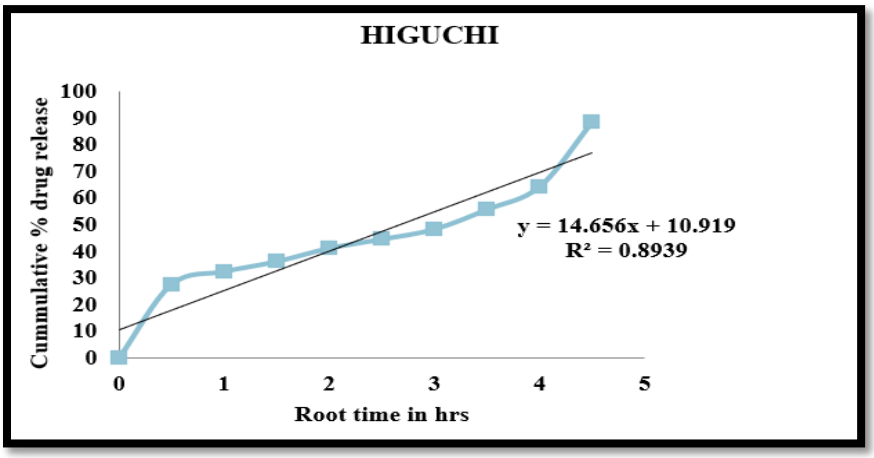

Fig 11: Diffusion profile (Higuchi plot) of formulation f6

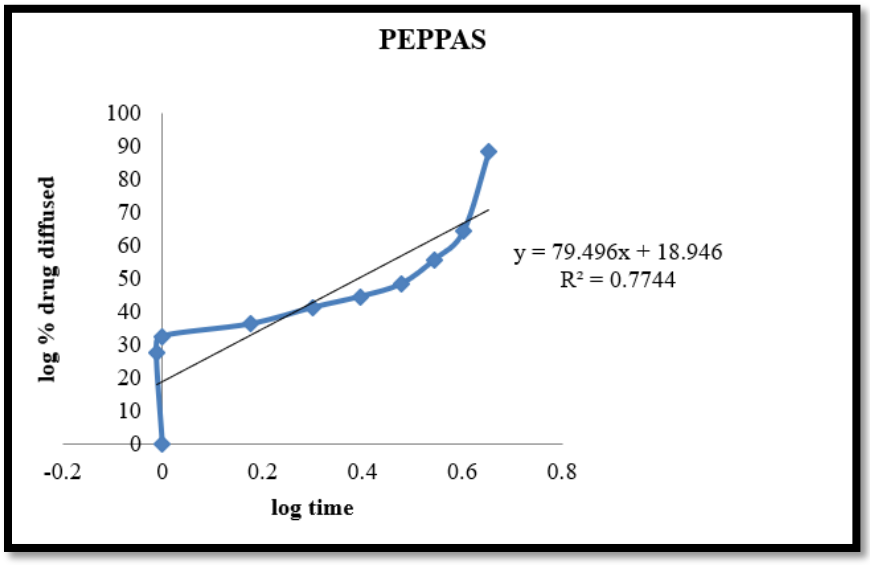

Fig 12: Peppas plot of formulation f6

Stability studies:

It is evident from the data that the transfersomes demonstrated the least amount of medication loss over a 30-day period at a temperature of 25°C. Both the percentage of drug content and the percentage of entrapment efficiency were relatively high.

Table 7: % Entrapment efficiency and % Drug content after stability studies

Number of Days	%Entrapment Efficiency at (25±2°C)		% Drug Content at (25±2°C)	
	Before	After	Before	After
30	91.87	89.66	92.04	91.26

CONCLUSION:

Meloxicam'sFTIR pre-formulation investigations conformed that there was no contact among the medication and excipients, according to the FTIR spectra. Thin film hydration was used to create the transfersome formulations, which were then added to the 1.5% carbapol gel. The Formulation F6 has a greater entrapment efficiency and maximum drug release since it contains Lecithin: Span-80 in a ratio of 89.84763 (%w/w). A greater correlation with Higuchi's equation was discovered to fit the kinetic analysis of the transfersome gel formulation than with the zero order and first order. This claims that diffusion process was primarily responsible for the drug's release from the lipid bilayer. According to stability studies for improved transfersome gel formulations, manufactured transfersomes are stable at room temperature. Finally, it can be inferred from the findings of the current study that transfersome gel enhances the transdermal distribution of the medication Meloxicam, prolongs the release, and improves site specificity. With the use of transfersomes, a number of medications that are difficult to administer through other methods can now be delivered safely and effectively transdermally.

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