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Preparation and In-Vitro Evaluation of Transferosome-Based Gel of Meloxicam

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ORIGINAL STUDY

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Preparation and In-Vitro Evaluation of Transferosome-Based Gel of Meloxicam

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Abstract

Objective: The present study aimed to enhance the effectiveness of meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), through topical application using vesicular drug delivery systems, focusing on several innovative formulation strategies. These strategies aim to improve the drug's solubility, skin permeation, and overall therapeutic efficacy while minimizing systemic side effects.

Method: A phospholipid bilayer made from egg lecithin and surfactants (Span 60 and Span 80) in varying ratios was used to develop a transferosome dispersion via a thin film method. This blend was then combined with the polymer Carbopol 934 to form a gel. The evaluation included both the transferosomal vesicles (including entrapment efficiency, vesicle size, polydispersity index, and zeta potential) and the transferosomal gel, assessing characteristics such as physical appearance, viscosity, spreadability, entrapment efficiency, drug content, and in vitro drug release to comprehensively characterize the final formulation.

Result: According to the evaluation results, F7 is the best formula since it has a good consistency and a pH level of 7.21 ± 0.13, which is acceptable for the skin. Further, it has a high drug content of 99.8% ± 6.4, an entrapment efficiency of 92% ± 1.3, and a good viscosity of 2354 ± 1.1. The drug release rate is also 98.7%.

Conclusion: The development of an optimized transfersomal gel for meloxicam using various edge activators and different ratios of egg lecithin has shown promising results in enhancing the properties of the formulation.

Keywords: Transferosome, Meloxicam, Egg lecithin, Edge activators, Topical application

1. Introduction

Meloxicam (MX) is a potent nonsteroidal anti-inflammatory drug (NSAID) commonly used for treating conditions like rheumatoid arthritis and osteoarthritis due to its effectiveness in reducing pain and inflammation with lower toxicity than that of other NSAIDs meloxicam inhibits COX-2 (cyclooxygenase-2) more than COX-1 (cyclooxygenase-1), but it can still cause significant gastrointestinal side effects when taken at high doses for extended periods. As a result, there is a strong need to administer meloxicam via an alternative route to enhance its solubility, reduce gastric adverse effects, and target delivery to the site of inflammation. The topical route is a delivery system that is more convenient to use and also administered by users. It is non-invasive and reduces oral side effects. However, its clinical application is limited by several factors, including low aqueous solubility, poor incorporation into formulations, and limited skin permeability. To address these challenges, drug carriers in vesicle systems are effective and efficient methods for delivering drugs to their targets. Different carrier systems, like liposomes, transferosomes, pharmacosomes, phytosomes, niosomes, solid lipid nanoparticles, microparticles, and nanoparticles, are being used for site-specific drug delivery and to prevent drug candidates from metabolic degradation. The major focus of this work is on how transferosomes prove to be an efficient carrier for targeted drug delivery. Drug molecules decompose due to

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various metabolic processes and other physiological conditions of the body; this creates the need for site-specific systems for drug delivery to protect the drug molecules. Transferosomes are vesicle systems used as carriers to deliver drugs or active substances across skin membranes. These vesicles are made from phospholipids and surfactants, designed to enhance drug delivery efficiency by improving skin permeation. Incorporating these vesicles into a gel formulation allows for better application and controlled drug release. This study evaluates several parameters, including physical appearance, pH, viscosity, spreadability, entrapment efficiency, drug content, and in vitro drug release. These evaluations indicate that the transfersome-based gel formulation could significantly enhance the skin permeation of meloxicam, potentially leading to improved therapeutic outcomes while minimizing gastrointestinal side effects associated with oral administration [1, 2].

2. Material and methods

2.1. Material

Meloxicam was purchased from Shanghai D&B Biological Science and Technology Co., Ltd. (China); Span 80 from Shanghai Tunchem Pharm (China); and Span 60 was obtained from Merck (Germany). Egg lecithin was sourced from Hyperchem (China); sodium hydroxide was obtained from Sigma-Aldrich (USA); methanol from Thomas Baker Pvt. Ltd. (India); and chloroform was purchased from GIBCO, Merelbeke (Belgium). Potassium dihydrogen phosphate was obtained from Hopkins and Williams Ltd. (England); dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich (USA). Carbopol-934 was supplied by HIMEDIA (India), and deionized water was sourced from Chem-lab (Belgium).

2.2. Identification tests

2.2.1. Melting point determination

The melting point of a drug is a critical parameter for assessing its purity, as impurities typically alter the melting point range. The Barnstead Electrothermal 9100, UK electrical melting point apparatus is designed to facilitate accurate melting point determination, which is essential in pharmaceutical quality control. The drug sample is loaded into a sealed glass capillary tube. This tube is essential for containing the sample and allowing for precise temperature measurements. The capillary tube is inserted into the device. As the temperature rises, the drug powder eventually melts. The endpoint of the process is marked by the observation of the melting point, which is recorded by the apparatus. The melting point of meloxicam should occur in the range of 254 °C – 256 °C [3].

2.2.2. Preparation of calibration curve in phosphate buffer

To create a calibration curve for meloxicam, phosphate buffer at pH 7.4 and DMSO were used. The drug was diluted to 1, 2, 3, 4, 5, and 6 mL from a stock solution of 0.5 mg/mL, and the total volume was adjusted to 10 mL using 10 mL volumetric flasks for each dilution. The absorbance of these diluted mixtures was measured with a UV-visible spectrophotometer (Biotech Engineering Management Company) and plotted against concentration to develop the calibration curve [4] and then determine the R2 value (correlation coefficient), this value measures strong the linear relationship between the concentration and the absorbance value. If the R2 value is equal to one, then that shows a perfect positive relationship.

2.3. Method

2.3.1. Preparation of meloxicam-loaded transferosome formulations

Eight formulations (EF1.EF8) were developed through the thin film hydration technique known as the Rotary Evaporation-Sonication Method. This approach effectively encapsulates both hydrophilic and hydrophobic drugs within lipid bilayers, improving the dissolution of the hydrophobic drug Meloxicam. We employed egg lecithin along with different types and proportions of edge activators to investigate their effect on the characterization of the prepared transferosome, as detailed in Table 1. The first step involved dissolving the lipid (egg lecithin) and edge activators (Span 60 or 80) in a solution of diethyl ether and chloroform in a round-bottom flask. The thin film was then created by evaporating the solvent at 50 °C using a rotary evaporator (Labinco, Netherlands). It is important to note that temperature plays a crucial role in the development of films; we found that the film did not form at temperatures below 50 °C or above 55 °C. A 1:1 solution of DMSO and phosphate buffer (pH 7.4) was also used to dissolve 100 mg of meloxicam, which was then heated to the same temperature as the film. To produce transferosomal suspensions, the film was hydrated for two hours using a rotary evaporator and then sonicated with a sonicator (Copley Scientific, U.K.) for two minutes [5, 6].

2.3.2. Preparation of carbopol gel

Carbopol polymers serve as effective gelling agents in transferosome-based medicines because they

Table 1. Composition of the transferosomal gel.

Formulation Code	Egg lecithin (%w/w)	Span 80 (%w/w)	Span 60 (%w/w)	Drug (%w/w)	Carpobol 934
EF1	2%	4%	_	1%	1%
EF2	3%	3%	_	1%	1%
EF3	4%	2%	_	1%	1%
EF4	5%	1%	_	1%	1%
EF5	2%		4%	1%	1%
EF6	3%		3%	1%	1%
EF7	4%		2%	1%	1%
EF8	5%		1%	1%	1%

control the release of the encapsulated drug specifically at the targeted site. By incorporating the transferosome into a gel formulation with Carbopol polymers, drug delivery to the deeper layers of the skin was significantly improved, enhancing contact duration while minimizing moisture loss from the skin. In this study, we prepared a 1% gel; 1 g of Carbopol 934 was weighed (this weight of the polymer will give good gel consistency), dissolved in 100 mL of distilled water, and allowed to swell for 24 hours then incorporated into transferosme suspension [7].

2.3.3. Preparation of transferosomal gel

One gram of the transfersome formulation was weighed using an electronic balance (Radawag Wagi, Poland Electroniczne), dissolved in ten milliliters of ethanol, and centrifuged using a digital centrifuge (EBA-20, Zentrifugen, HeHich lab Technology, Germany) for twenty minutes at 6000 rpm. After decanting the supernatant, mechanical mixing at 25 rpm was used to integrate the sediment into the gel vehicle [8].

2.4. Evaluation tests of deformable transferosome

2.4.1. Entrapment efficiency of transferosome (%EE)

Dissolve a specific amount of each prepared formula in phosphate buffer to a final volume of 10 ml. Centrifuge the solution for 50 minutes at a speed of 15,000 rpm. Carefully collect the supernatant after centrifugation. This liquid contains the unentrapped drug. Dilute the supernatant with the appropriate amount of phosphate buffer to ensure it is within the measurable range for analysis. Measure the absorbance of the diluted supernatant using a UV-visible spectrophotometer at the wavelength corresponding to λ max for the drug [9].

The percent entrapment efficiency (%EE) was calculated using the following equation:

(10) %EE = (Total drug Free drug)/Total drug × 100.

2.4.2. Vesicle size, polydispersity index, and zeta potential of transfersomes

When preparing and evaluating transferosomes, it's essential to measure their vesicle size, polydispersity index (PDI), and zeta potential to assess their stability, uniformity, and drug delivery efficiency. These parameters are critical in determining the effectiveness of transferosomes, especially in topical or transdermal drug delivery systems. The vesicle size of transferosomes preferred for topical or transdermal applications ranges from 50 to 200 nm, as they are more likely to penetrate the skin barrier. The size affects the drug release rate, skin penetration, and interaction with skin receptors. It can be determined by using dynamic light scattering (DLS) (Brookhaven, USA). The distribution of vesicle size within the sample can be determined by PDI measurement, while the surface charge of the vesicle can be measured by zeta potential. Zeta potential is typically measured using a Zetasizer (Malvern Panalytical, UK) [10].

2.5. Evaluation tests of transferosome gel

2.5.1. Physical appearance of transferosomal gel

This test will be done visually for all prepared formulas (EF1-EF8) to evaluate their color and homogeneity. Observe and note the color of each formula. Look for consistency in color and any variations that may indicate issues in the formulation. Gently mix each formula to check for uniformity. A homogeneous formula should appear consistent throughout, without visible phase separation or sediment [11].

2.5.2. pH determination of transferosomal gel

Weigh 0.5 g of each transferosome-based gel formula (EF1 to EF8). Dissolve the weighed sample in 50 mL of distilled water. Ensure thorough mixing to achieve complete dissolution. Allow the solution to equilibrate for 2 minutes. Use a calibrated digital pH meter (Hanna Instruments, Italy) to measure the pH of the solution. Rinse the pH probe with distilled water before and after each measurement to ensure

accuracy. Finally, record the pH values for each formula (EF1 to EF8) for further analysis [12].

2.5.3. Spreadability test of transferosomal gel [13]

A spreadability test is necessary for topical preparations, ensuring the product is easy to apply on the skin. Spreadability consists of expanding a semi-solid formulation on a surface after a certain time. In this study, three grams of each gel formula (EF1 to EF8) should be placed between two glass slides. Record the initial diameter of the spread circle without applying any weight, set a weight pan on top of the upper glass slide, and allow the setup to sit for 10 minutes to observe spreading. Measure the diameter of the spread circle after the 10 minutes have elapsed, ensuring no further spreading occurs. Each formula's spreadability (S) can be found using the following equation:

$$S = m * l/t$$

Where:

S = sample spreadability

m = upper plate weight (g)

l = glass plate length (cm)

t = time required for the sample to spread (in minutes).

2.5.4. Viscosity test of transferosomal gel

The viscosity of transferosome formulas (EF1-EF8) was measured using a Brookfield viscometer with spindle number S-62 at a temperature of 37 °C. The measurements were taken after 30 seconds of operation. For accurate viscosity readings, it is essential to ensure that the viscometer is calibrated correctly and that the samples are prepared consistently. The viscosity data obtained can provide insights into the flow properties of the transferosome formulations, which are crucial for their application in drug delivery systems [14].

2.5.5. Drug content of transferosomal gel

Weigh 1 gram of each prepared formula (EF1 to EF8) and combine it with 100 mL of ethyl alcohol to form a solution. Filter this solution to eliminate undissolved particles, ensuring clarity for further analysis. Make appropriate dilutions from the filtered solution to create aliquots of different concentrations. This process is essential for achieving a range of absorbance values needed to construct the calibration curve. Measure the absorbance of each diluted aliquot at a wavelength of 375 nm using a UV-visible spectrophotometer [15].

2.5.6. In vitro drug release

The in vitro drug release study you described utilizes a Type II dissolution apparatus (Campbell Electronics, India), which is commonly employed for testing the release of drugs from various formulations, including gels. In your setup, a 1 g sample of transferosomal gel is sealed in a dialysis bag and submerged in 500 mL of phosphate buffer at pH 7.4 (it mimics the physiological pH of human blood) maintained at a temperature of 37 °C (essential for ensuring that the conditions reflect the human body's internal environment, which can significantly affect drug solubility and release rates. The solubility of meloxicam is higher in phosphate buffer pH 7.4 due to ionization of the drug) with a rotation speed of 50 rpm to ensure uniform drug distribution and prevent localized saturation. Regularly withdrawing 5 mL of the dissolution medium and replacing it with an equal volume of fresh phosphate buffer helps maintain sink conditions and minimizes the risk of saturation in the dissolution medium. Each sample is analyzed using UV spectroscopy to determine the λ max (lambda max) of the drug, ensuring accurate monitoring of drug release [16].

2.6. Selection of best transformal gel formula

The selection of an effective formulation depends on the evaluation tests of different formulas. Suppose a formula demonstrates good physical appearance, appropriate viscosity, excellent spreadability, high entrapment efficiency, adequate drug content, and a favorable in vitro release profile. In that case, it can be considered a suitable choice.

3. Result and discussion

3.1. Identification test

3.1.1. Melting point determination

The melting point of meloxicam was determined to be 254 °C, which aligns with standard data. This consistency indicates a high purity of the meloxicam powder, suggesting that it is free from significant impurities that could alter its melting characteristics [17].

3.1.2. Calibration curve determination

The calibration curve of meloxicam in phosphate buffer (pH 7.4) is illustrated in Fig. 1. A straight line was obtained by plotting the absorbance against concentration, yielding a high regression coefficient (R^2). This result demonstrates that the calibration

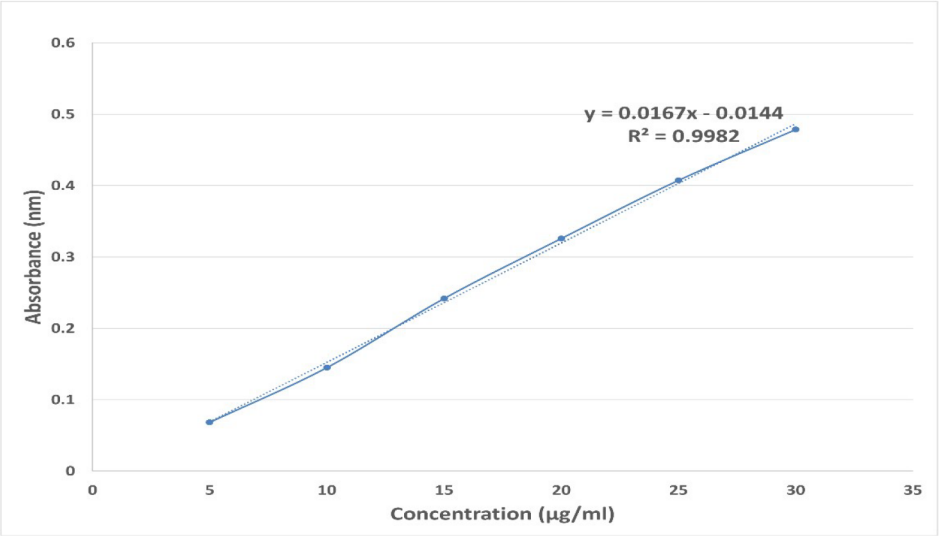

Fig. 1. Calibration curve of meloxicam in phosphate buffer PH 4.7.

Table 2. Result of % entrapment efficiency, vesicle size, PDI, and zeta potential of transfersomes.

Formulation code	Entrapment efficiency	Vesicle size	PDI	Zeta potential
F1	63% ± 1.9	241 ± 3	0.256 ± 0.015	−32.6 ± 3
F2	70% ± 1.6	243 ± 5	0.346 ± 0.03	−36.2 ± 2
F3	92% ± 1.4	250 ± 2	0.292 ± 0.02	−37.5 ± 4
F4	93% ± 1.8	264 ± 3	0.511 ± 0.03	−34.4 ± 2
F5	94% ± 1.2	253 ± 2	0.489 ± 0.04	−35.5 ± 6
F6	89% ± 2.5	270 ± 6	0.423 ± 0.02	−38.5 ± 2
F7	92% ± 1.3	261 ± 4	0.392 ± 0.015	−33.4 ± 4
F8	91% ± 1.5	271 ± 3	0.521 ± 0.03	−39.5 ± 2

curve adheres to Beer's law within the tested concentration range.

3.2. Evaluation test of deformable transferosome

3.2.1. Entrapment efficiency (%EE) of transferosome

The results are shown in Table 2. Most of the outcomes are positive, indicating that the thin-film method used in the preparation was effective.

3.2.2. Vesicle size, polydispersity index, and zeta potential of transfersomes

The results show that the ranges of the vesicle size of all transferosomal formulas were 241 ± 2.5 to 272 ± 3 nm, with a PDI of vesicle distribution ranging from 0.256 ± 0.015 to 0.521 ± 0.03. The index being less than one indicates a narrow size distribution (uniform vesicle size) within the preparation. The zeta potential values of transfersomes in the study were found to be in the range of −32.6 ± 3 to −39.5 ± 2 mV, indicating the stability of the prepared formula, as shown in Table 2.

3.3. Evaluation test of transferosome gel

3.3.1. Physical appearance

The consistent appearance of drug formulations, particularly those exhibiting a homogeneous white color, is crucial for ensuring quality and stability. A uniform color indicates that the formulation is well mixed and that the active pharmaceutical ingredients (APIs) are evenly distributed throughout the product. This is essential for maintaining the efficacy and safety of the medication.

3.3.2. pH determination

The pH values of the formulated preparations, ranging from 6.95 to 7.21, are well within the optimal range for topical skin applications. This pH range is crucial as it helps to minimize the risk of skin irritation, which is particularly important for formulations intended for sensitive skin areas. The optimized formula (F7) with a pH of 7.21 aligns with these requirements, indicating that it is suitable for application on the skin without causing adverse reactions [18], as shown in Table 3.

Table 3. Result of test evaluation of transferosomal gel formulation.

Formulation cod	pH	Spreadability (Gm.cm/sec.)	Viscosity (cps)	Drug content (%)
F1	6.95 ± 0.12	11.10 ± 0.12	2518 ± 0.8	95.65 ± 0.12
F2	6.98 ± 0.8	11.65 ± 0.98	2332 ± 0.5	95.45 ± 0.25
F3	7.12 ± 0.15	12.21 ± 0.13	2280 ± 1.3	96.98 ± 0.15
F4	6.99 ± 0.9	11.47 ± 0.83	2094 ± 1.5	96.56 ± 0.25
F5	6.97 ± 0.12	12.43 ± 0.14	2301 ± 1.5	97.23% ± 0.14
F6	7.20 ± 0.08	12.50 ± 1.20	2286 ± 1.1	97.03% ± 0.3
F7	7.21 ± 0.13	12.65 ± 0.16	2354 ± 1.1	99.8% ± 6.4
F8	7.00 ± 0.18	13.25 ± 0.92	2133 ± 1.3	97.83% ± 0.7

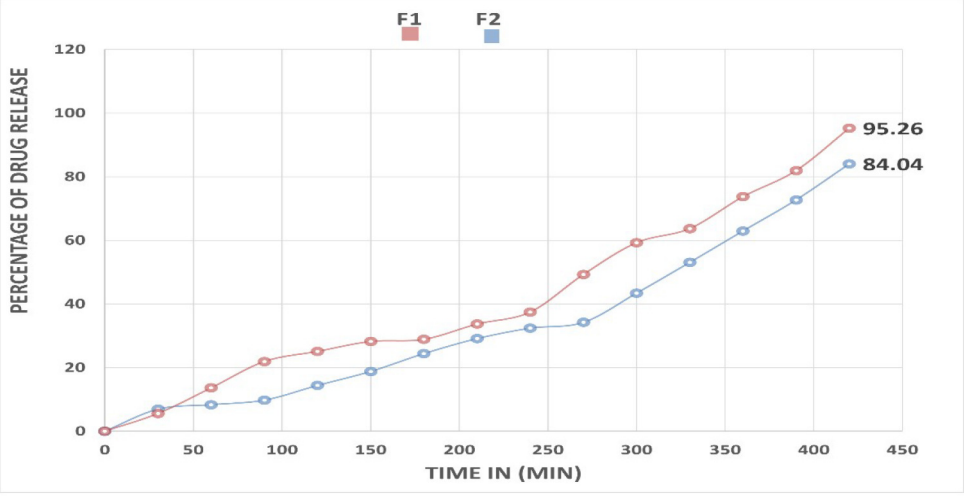

Fig. 2. Cumulative % drug release Vs time for F1 and F2.

3.3.3. *Spreadability test*

The spreadability values ranging from 11.1 to 13.25 gm/cm/sec indicate variability among your formulations. Highlighting the optimized formula (F7) at 12.65 gm/cm/sec shows that it performs well compared to the others. A higher spreadability value typically means easier application and better coverage on the skin. This characteristic is crucial for patient compliance, as formulations that spread easily are generally preferred, as shown in Table 3.

3.3.4. *Viscosity test*

The viscosity measurements obtained using a Brookfield viscometer provide valuable insights into the formulation characteristics of transfersomal gel. The favorable viscosity of the optimized formula (F7) can indeed be linked to the edge activator ratio, particularly the use of nonionic surfactants. As the ratio of edge activators increases, the viscosity of the formulation also tends to increase. This is likely due to the enhanced interactions between the surfactants and the phospholipid matrix, which contribute to a more stable and viscous gel structure [19]. The results of the viscosity test are shown in Table 3.

3.3.5. *Drug content*

The percentage of drug content for the meloxicam formulations, ranging from 95.65% to 99.80%, reflects a high level of adequacy in the preparation method. This range indicates that the formulations effectively incorporate the active ingredient, which is crucial for ensuring therapeutic efficacy. As shown in Table 3.

3.3.6. *In vitro drug release*

The in vitro drug release of the formulas was conducted in a phosphate buffer with a pH of 7.4. Cumulative drug release was measured at different time intervals, as shown in Figs. 2 to 4. The results for formulation F7 showed a maximum drug release of 98.7%, which is higher than that of the other formulations. Although F7 demonstrated a slightly greater amount of drug release than F8, this can be attributed to F7 containing a higher concentration of Span 60. This increased concentration affects the integrity of the lipid membrane, making

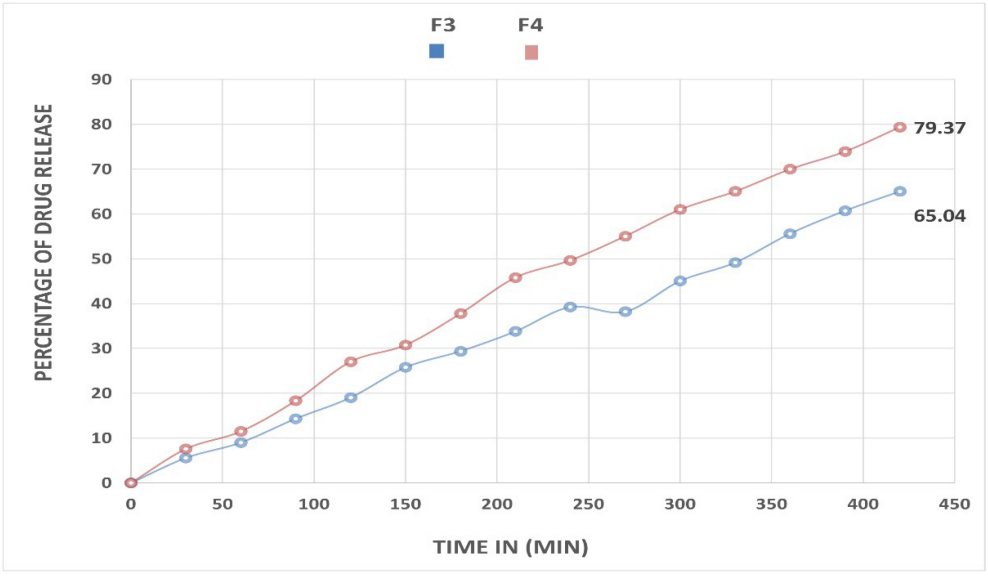

Fig. 3. Cumulative % drug release Vs time for F3 and F4.

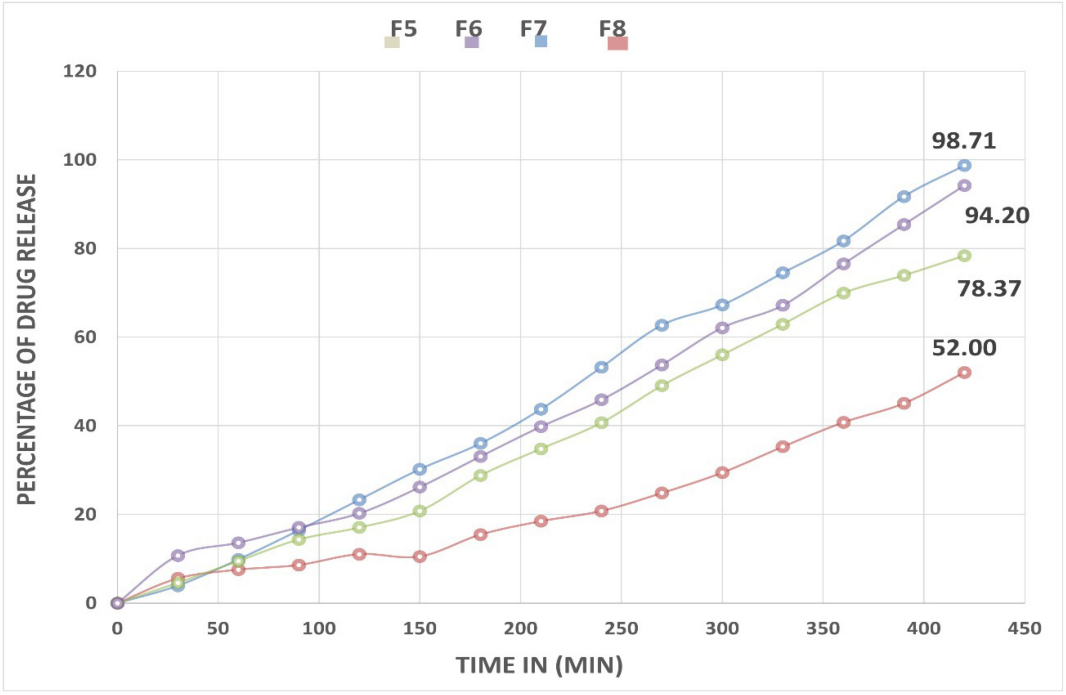

Fig. 4. Cumulative % drug release Vs time for F5, F6, F7 and F8.

it more permeable and resulting in enhanced drug release [20].

4. Conclusion

Meloxicam (MEL) is a selective cyclooxygenase inhibitor from the enolic acid drug class, known for its analgesic and antipyretic properties. This medication appears as a white, crystalline, and odorless powder, which is soluble in organic solvents such as DMSO. A significant side effect associated with meloxicam is gastrointestinal irritation. Transfersomes are vesicular systems designed to transport drugs or active compounds through skin membranes. Utilizing this delivery system can enhance drug solubility, enhance drug penetration, and reduce gastrointestinal side effects. The melting point is 254 °C. Eight different formulations were prepared using varying amounts

of egg lecithin, Span 60, Span 80, and the drug, and evaluated for entrapment efficiency. These were then formulated as a gel using Carbopol as a polymer and evaluated for pH, viscosity, spreadability, drug content, and in vitro drug release. The optimized batch of transfersomes was F7. Drug content is the most important aspect in transfersomes formulation, and the data found are satisfactory, ranging from 95.65% to 99.80%, which shows the good capacity of the formulation to hold the drug. The maximum drug content was found in formulation 7 (99.80%).

Future applications

In the future study,

1- Further pharmaceutical studies such as stability
2- Clinical trials on animals and then humans to prove the efficient therapeutic activity of the product as well as a complete toxicity study
3- More details about the most suitable storage conditions for such products.

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