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Preparation and evaluation of transdermal gel loaded with spanlastics containing meloxicam

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ABSTRACT: A transdermal drug delivery system (TDDS) is characterized by the application of medications onto the skin's surface to deliver drugs at a controlled and predefined rate through the skin. Spanlastics, an elastic nanovesicle capable of transporting various pharmacological substances, shows promise as a drug delivery carrier. It offers numerous advantages over traditional vesicular systems applied topically, including enhanced stability, flexibility in penetration, and improved targeting capabilities. This study aims to develop meloxicam (MX)-loaded spanlastics gel as skin delivery carriers and to look into the effects of formulation factors like Tween80, Brij 35, and carbopol concentration on the properties of spanlastics gel, like pH, drug content, extrudability, spreadability diameter, viscosity, and release profiles in addition to Ex vivo skin permeation for optimal formula. The optimal formula of spanlastics gel (GF1) shows acceptable pH (6.2±0.14), excellent extrudability(92%), drug content (97.1±0.14), spreadability diameter (cm) (10.8±0.28), sustained release 70.7±0.57% for six hours and the steady-state flux of meloxicam through rat skin was increased 83.52-fold as a result of spanlastics in comparison to the plain gel. The vesicles produced in this investigation could potentially interact with or merge with the stratum corneum as a result of their elasticity, which may also be the mechanism that increases the penetration into the skin. According to our findings, dermal delivery vehicles for MX may be provided via spanlastics gel.

KEYWORDS: Meloxicam; spanlastics gel; transdermal drug delivery; transdermal gel.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) are widely utilized in the pharmaceutical industry due to potential advantages over traditional delivery methods like injections and oral ingestion [1]. Transdermal meloxicam administration provides a notable benefit in addressing arthritic conditions by avoiding the digestive system and facilitating a greater concentration of the drug at the local site [2].The main challenge with TDDS lies in the skin's limited permeability to large molecules and hydrophilic drugs while being permeable to smaller molecules and lipophilic medications [3]. To overcome this barrier and prolong drug retention in skin layers, researchers have explored the use of elastic vesicular nanocarriers known as Spanlastics [4]. Spanlastics represent a novel drug delivery approach that combines vesicular and nanoparticulate properties. The term "Spanlastic" is derived from "span add to elastic," reflecting the core medication enclosed within a bilayer structure [5, 6]. The spanlastics are primarily composed of non-ionic surfactants and edge activators (EAs) such as tweens, polyvinyl alcohol, and Brij, developed by Kakkar and Kaur. These surfactant-based deformable nanocarriers [5, 7]. EAs play a crucial role in disrupting the membranes of nanocarrier vesicles, thereby improving their flexibility and enabling them to pass through diverse pores in biological layers without breaking. Importantly, nanospanlastics are both nontoxic and biodegradable, making them a promising option for drug delivery [8].

2. RESULTS and DISCUSSION

2.1. Physical characteristics

The MX- spanlastics gel was discovered to be off-white with a viscous smooth and uniform texture, lacking grit or phase separation.

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2.2. PH of the MX- spanlastics gel

The pH values of the developed MX-Spanlastics gel formulations are shown in Table 1. It was revealed that MX-Spanlastics Gel has a pH between 5.6 and 6.5, it is comparable to the skin's pH to prevent skin irritation [9].

2.3. Spreadability

A good spreadability value is an important characteristic of the gel dosage form[10]. According to the data provided in Table 1, a Carbopol concentration of 940 has a beneficial influence on spreadability (greater concentration of Carbopol 940 might minimize spreadability). These findings were comparable to those of Safitri *et al*. [11].

2.4. Drug content

The uniformity of all the MX-Spanlastics gel formulations made for this study, which ranged from (96.85%±0.21) to (98.95%±0.49) was determined to indicate that the medication was not lost or changed.

Table 1. Value of Measured pH, Drug content, Extrudability, and Spreadability diameter for MX-spanlastics gel Formulations

Formulation code	pH	Drug content	Extrudability / Interpretation [12]	Spreadability diameter (cm)
GF1	6.2±0.14	97.1±0.14	92% / Excellent	10.8±0.28
GF2	5.7±0.14	98.95±0.49	71% / Fair	6.5±0.70
GF3	6.1±0.28	96.85±0.21	90% / Excellent	11.9±0.42
GF4	5.65±0.21	98.25±0.35	73% / Fair	6.7±0.42

2.5. Viscosity

As shown in Figure 1 below the viscosity of the gel lowered as the shear rate rose, showing a shear-thinning pseudoplastic flow feature [13,14]

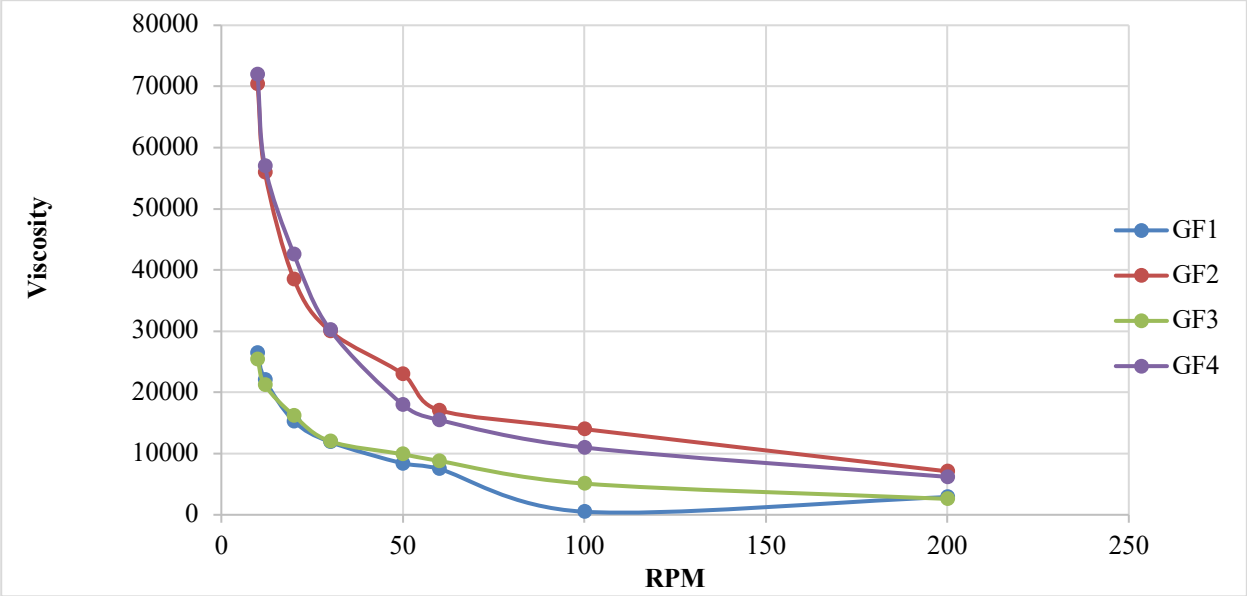

Figure 1. Viscosity analysis of MX-loaded spanlastics gel formulations.

2.6. Release of MX-loaded spanlastics gel in vitro

All prepared formulas as shown in Figure 2 below showed slower release profiles of MX from the spanlastics gel this could be attributed to carbopol's excellent thickening, emulsifying, suspending, and gelling properties [15].

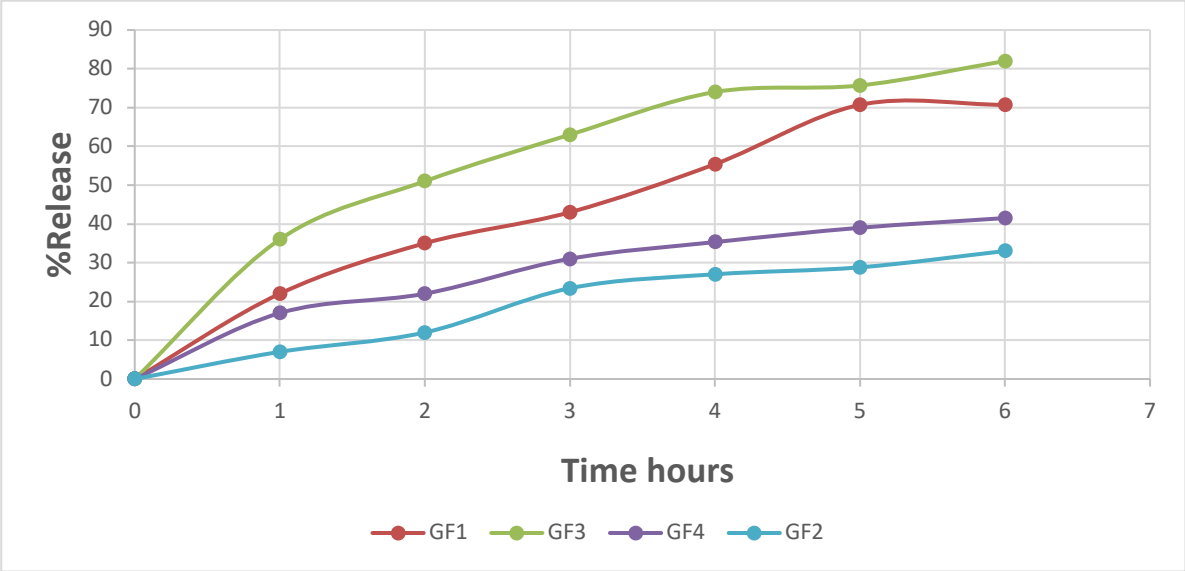

Figure 2. Release profiles analysis of MX-loaded spanlastics gel formulations

2.6.1. Effect of type of edge activator on the percentage of drug release

There is a significant difference (p≤0.05) in the release profiles of MX from spanlastics gel**.** Formulation containing Brij®35 exhibited the highest release profiles (82±2.82% and 41.5±0.707%) for GF3 and GF4 respectively compared to those containing Tween®80 which had release profiles (70.7±0.57% and 33±0.7%) for GF1and GF2 respectively**.** This can be explained by the fact that spanlastics have a release that is dependent on the length of the alkyl chain; the slower the release rate, the longer the chain length, Similar outcomes were found in niosome-encapsulated gentamicin by Abdelbary *et al.* [16].

2.6.2. Effect of Carbopol concentration on the percentage of drug release

Regarding the effect of carbopol concentration on the percentage of MX release in the case of (GF1, GF3) which had release profiles (70.7±0.57% and 82±2.82%) respectively in comparison to (GF2, GF4) which had release profiles (33±0.7% and 41.5±0.707%) respectively, there is a significant difference (p ≤ 0.05) in release profiles of MX from spanlastics gel. The percentage of drug release decreased as the percentage of gelling agents rose [13, 17,18].

2.7. Modeling of release kinetic

The release of meloxicam from various spanlastics formulations was simulated using a variety of mathematical models. Table 2 lists the values of the regression coefficients and release constants.

Table 2. Summarized results for release kinetics.

Formula code	Zero-order		First order		Higuchi model		Korsmeyer-Peppas model		
	K_0	R^2	K_1	R^2	kH	R^2	K_{kp}	n	R^2
GF1	13.436	0.9353	0.213	0.9861	28.059	0.9612	21.558	0.688	**0.9879**
GF3	16.412	0.7421	0.332	0.9772	35.018	0.9909	37.840	0.444	**0.9945**
GF2	6.057	0.9469	0.072	0.9698	12.559	0.9183	8.482	0.779	**0.9709**
GF4	8.123	0.8306	0.105	0.9175	17.203	0.9935	16.708	0.521	**0.9939**

The Korsmeyer-Peppas model was determined to be the best-fit model for understanding MX release from spanlastics gel formulations based on Table 2 since it had the highest R^2 values for all formulas that were tested. Similar results for drugs released from Transfersomes have been reported by Khan *et al.* [19]. With the exception of GF3, where the n value is less than 0.5, signifying quasi-Fickian drug transport, all other formulas exhibited exponents (n values) greater than 0.5, suggesting that the drug transport mechanism closely approximates non-Fickian diffusion.

2.8. In vitro permeation test

The steady-state flux, Jss, was determined by analyzing the slope of the line in Figure 3 below. It's evident from the data that the steady-state flux for Spanlastics gel formula (GF1) stands at 14.258 µg/cm2/h, while for the plain gel, it's 0.1707 µg/cm2/h. By applying equation 1, the apparent diffusion coefficients, Papp, for the optimal Spanlastics gel (GF1) and plain gel were calculated as 5.7 × 10-3 cm/h and 0.068 × 10-3 cm/h, respectively.

The incorporation of spanlastics resulted in a remarkable 83.52-fold increase in the steady-state flux of meloxicam through rat skin. This enhancement can be attributed to several factors, as explained by Agrawal *et al* and Farghaly *et al*.: the presence of non-ionic surfactant Span® 60 within spanlastics, which functions as a penetration enhancer due to its excellent interaction with skin layers, facilitated by its low HLB value (HLB = 4.7). Additionally, the flexible structure of these vesicles allows for more efficient skin penetration while maintaining drug integrity during the permeation process [4,20].

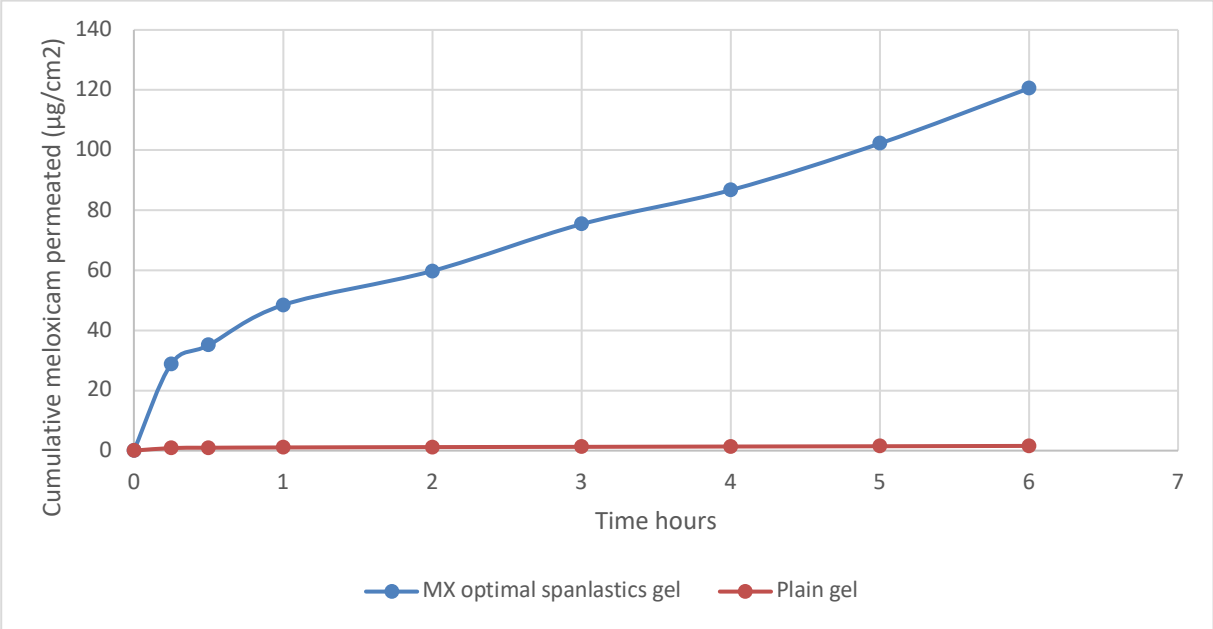

Figure 3. Permeation profile of meloxicam across the rat skin

2.9. FTIR spectrum of the optimum MX-loaded spanlastics gel

Pure meloxicam major bands are 3286.7, 1620.21, 1527.62, and 1184.29 cm^{-1} that is due to N-H stretching vibration, NH2 scissoring vibration, C=N stretching vibration, and S=O stretching vibration, respectively. This was in agreement with previously published articles [21- 23].

The (N-H stretching vibration) in the physical mixture's FTIR spectrum shows a minor shift from 3286.70 cm^{-1} to 3290.56 cm^{-1}, but the other major peaks show no changes. This shows that there is no interaction between meloxicam, carbopol940, and the components used to make the MX-loaded spanlastics gel.

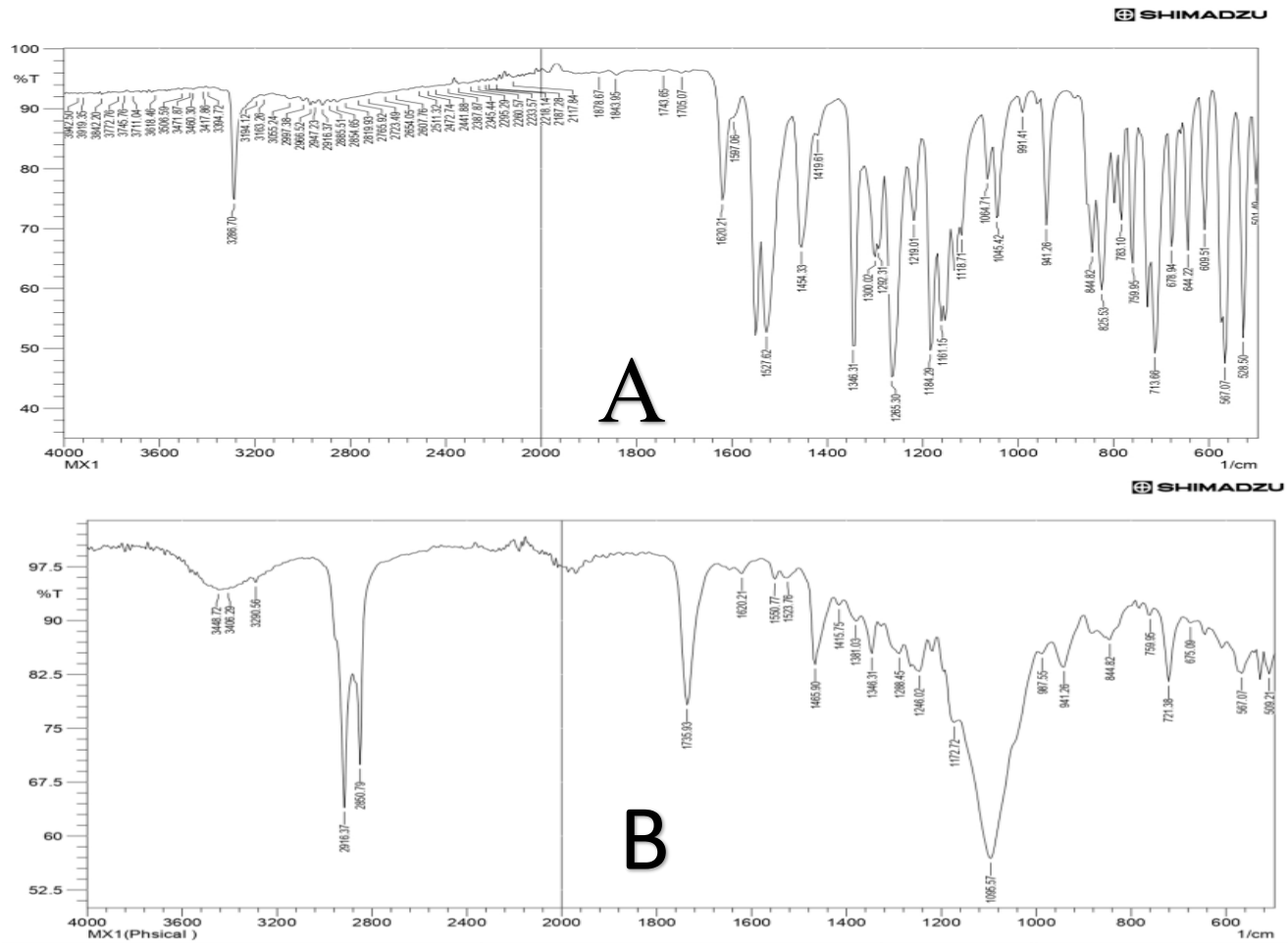

Figure 4. F.T.I.R. spectrum of meloxicam (A) and physical combination (B)

3. CONCLUSION

According to the study's findings, MX-spanlastics gel was successfully created, and formulation parameters such Tween®80, Brij® 35, and Carbopol content had a positive impact on the gel. Optimal formula (GF1) demonstrated better MX skin penetration than MX-plain gel when given with spanlastics gel, overcoming the skin's barrier characteristics to promote the anti-inflammatory activity of meloxicam while avoiding oral issues, resulting in improved patient compliance.

4. MATERIALS AND METHODS

4.1. Materials

Meloxicam MX powder (Baoji Guokang Bio-Technology Co., Ltd), Span 60 (Xi'an Sonwu Biotech Co.Ltd, China), Brij35 (Shanghai Macklin Biochemical Co., Ltd, China), Tween 80 (Thomas baker, Mumbai, India), Methanol (Thomas Baker, India), Ethanol (Sasma, Netherlands), Chloroform (Thomas baker, Mumbai, India), Phosphate buffer saline pH 7.4 (PBS)(Himedia, India), Dialysis membrane M.wt 8000-14000(Special products laboratory, USA), Carbopol 940 (Hengshui Taocheng Chemicals Auxiliary Co., Ltd. China).

4.2. Methods

4.2.1. Preparation of MX-loaded spanlastics

Ethanol injection method is used to prepare spanlastics. The MX and the appropriate quantity of Span®60 were dissolved in the organic phase (consisting of chloroform and ethanol with ratio of 4:2), while the various formulations of Tween®80 and Brij®35 as EA were dissolved in 15 mL of deionized water at a temp. of 65°C as given in Table 3. A homogenizer was used to mix the aqueous solution at a speed of 2000 rpm for 15 minutes while the organic solution was added dropwise (1 ml/ min). The completed mixture was

held on the magnetic stirrer at room temperature for an additional 1.15 hours at a speed of 1000 rpm. The formulations were then stored in a refrigerator until more research was done on them [24].

Table 3. MX- loaded spanlastics composition.

Formula code	Drug (mg)	Span® 60(mg)	Tween®80 (mg)	Brij®35(mg)	Volume of the internal (organic) phase (ml)	Volume of the external phase (ml)
F1	15	350	39	__	6	15
F2	15	350	__	39	6	15

4.2.2. Preparation of spanlastics gel containing meloxicam and plain gel

After the preparation of MX-loaded spanlastics by ethanol injection method, A specified amount of MX-spanlastics dispersions was spun for 90 minutes at 4˚C and 20,000 rpm in a cooling ultracentrifuge[25]. The semisolid spanlastic mass equivalent to (0.5 % w/w) was removed from the supernatant and then incorporated in carbopol 940 with different percentages (1% and 2%). Using a mechanical stirrer, carbopol dissolved in double distilled water at the desired concentration, and the gel bases were then created. To reach the necessary skin pH level, a few drops of triethanolamine were introduced into the formulation. To get the final concentration of 0.5% of meloxicam spanlastic gel, the gel was combined with the resulting semisolid spanlastic of MX [26,27].

On the other hand, MX was dissolved in a 5% propylene glycol solution to create MX plain gel, which was created at a concentration of 0.5% (w/w). To achieve a homogeneous dispersion, carbopol was shaken continuously in distilled water using a stirrer at 1000 rpm. To obtain a homogeneous dispersion of MX gel, carbopol was continuously stirred into a 0.5% (w/w) MX solution [28]. All spanlastics gel Compositions are listed in table 4

Table 4. MX - spanlastics gel Composition.

Formulation code	**Carbopol 940 (%w/w)**	**MX spanlastics usingTween®80 (%w/w)**	**MX spanlastics using Brij®35 (%w/w)**	**MX powder (%w/w)**	**Propylene glycol (%w/w)**	**Distilled water**
GF1	1%	0.5%	__	__	__	Up to 100
GF2	2%	0.5%	__	__	__	Up to 100
GF3	1%	__	0.5%	__	__	Up to 100
GF4	2%	__	0.5%	__	__	Up to 100
MX plain gel	1%	__	__	0.5%	5%	Up to 100

4.2.3. Evaluation of MX spanlastics Gel

Physical appearance

All prepared spanlastic gels were visually examined for homogeneity after being placed in the container. They received an examination to look for aggregates and appearance [29].

Measurement of pH

A precise measurement of one gram of gel was dissolved in 100 milliliters of sterile water. To assess the pH of the resulting dispersion, a digital pH meter was employed, and the glass electrode was immersed into the gel composition [30] **.** The analysis was conducted three times for validation [31].

Measuring Drug Content

Precisely measuring 1 gram of MX-spanlastics gel, which contains 5 mg of MX, was introduced into a 50 ml volumetric flask containing pH 7.4 phosphate-buffered saline. After a 30-minute sonication, the solution was left to stand overnight. To determine the medication's concentration, the absorbance at 362 nm was quantified using a UV-visible spectrophotometer [32].

Determination of Extrudability

The force required for material extrusion from the tube is a common test. In this case, 30 grams of MX-spanlastics gel were loaded into a feeding syringe and sealed at the top. A weight of 1 kg was applied for a duration of 30 seconds. The quantity of extruded gel was collected and weighed, and subsequent calculations were performed to ascertain the percentage of the extruded gel [33, 34].

Spreadability determination

Two grams of MX-spanlastics gel were weighed and placed between two glass plates (14X14 cm). A load weighing 500 g was placed on the upper glass plate. After the application of weight waiting for five minutes and diameter were recorded. It was seen that the gel spreading caused the diameter to grow [35].

Viscosity determination

Using spindle no. 7 and Myr digital rheometer, the viscosity and rheology behavior of MX spanlastics gel formulations were tested at room temperature [36].

In vitro release study

The chosen spanlastics gel formulations were subjected to in vitro drug release. The amount of medication released after six hours was calculated using the dialysis bag method [26]. Briefly, from the chosen spanlastics gel formulations, a total of one gram of the gel (equivalent to 5 mg of MX) was obtained and placed into dialysis bags (which had been soaked in the release media overnight). The dialysis bags were then put in a paddle-style (type II- dissolution apparatus) with 250 ml of a PBS solution as the release medium to create a sinking state depending on our performed MX saturated solubility study in PBS which was found to be 0.421±0.83 mg/mL.

The paddles rotated at a rate of 100 revolutions per minute (RPM), and the apparatus temperature was maintained at 37 ±0.2 °C. At time intervals (1, 2, 3, 4, 5, and 6 hours), (3ml) was taken out and replaced with a fresh PBS solution [1].

By measuring the absorbance of MX at 362, its λ_{max}, in PBS and depending on the calibration curve equation (y = 0.051x - 0.0054) of MX that had previously been constructed in PBS by measuring the absorbance of different known MX concentrations and then plot them versus each other. The plot showed a straight line with a high correlation coefficient (R^2=0.9995). The release experiments were carried out in triplicate.

Kinetic models

To get the mechanism and kinetics of meloxicam release from spanlastics formulations, the collected in-vitro release data from several spanlastic formulations were fitted to several kinetic equations using the DDsolver and Microsoft Excel® 2016 programs [37]. In this method, four kinetic models[19,38], i.e. zero-order, first-order, Higuchi and Korsmeyer's -Pappas kinetic models.

In vitro permeation test

Using abdominal rat skin, diffusion cell with an effective diffusion area of 1.767 cm^2 was utilized for the study [39]. To ensure a sink condition, 12 ml of PBS with a cosolvent (20% methanol) was added to the receptor compartment, based on our prior MX saturated solubility study in PBS containing the same cosolvent (20% methanol), which showed a solubility of 2.3125 ± 0.7 mg/mL. A prepared skin sample was then positioned between the donor and receptor compartments. Maintaining the temperature at 37 ± 0.5°C and stirring at 100 rpm, we allowed 15 minutes for the membrane's temperature to stabilize[p6]. Subsequently, an amount equivalent to 2500 µg of the chosen MX-spanlastics gel and the plain gel was introduced into the donor compartment.

At regular intervals of 0.25, 0.5, 1, 2, 3, 4, 5, and 6 hours, 1 ml of the receptor compartment was withdrawn and replaced with fresh PBS containing a cosolvent (20% methanol) to maintain a constant solubility condition. The quantities of meloxicam that permeated during each time interval were quantified spectrophotometrically by measuring the absorbance at meloxicam's maximum wavelength in PBS.

The permeation profile of meloxicam from selected spanlastics gel and the plain gel was displayed as a graph, where the Y axis represents the amounts of meloxicam permeated per unit area and the X axis represents time. The steady-state flux JSS was determined by taking the slope of the straight line obtained from the permeation profile graph[19][40].

The evident permeability coefficient Papp was calculated using the equation shown below[41].

Papp = Jss/Co ……. Equation (1)

Where Co is the starting drug concentration in the donor compartment, Jss is the steady state flux, and Papp is the apparent penetration coefficient.

FTIR spectrum for the optimum MX-loaded spanlastics gel formula

FTIR spectrum for the pure drug (meloxicam) and the physical mixture which contains Tween® 80, span® 60, and carbopol940. Tested samples were placed immediately, without any prior preparation, onto the crystal area of Fourier transform infrared (FTIR) spectroscopy (Shimadzu, Japan) that combined with the attenuated total reflectance (ATR) approach. The pressure arm was then placed above the sample and scanned with an 8 cm resolution covering the range of 4000 to 400 cm-1 wavenumber [42]. This was done to test the compatibility between the materials used in the preparation of MX-loaded spanlastics gel [43].

Analytical statistics

The experimental data were assessed using the ANOVA statistical test through SPSS® version 26.0.0.0 software. Significance was determined with a threshold of $p \leq 0.05$, indicating significance, while $p > 0.05$ indicated non-significance. The results were represented by the mean of triplicate sample readings along with their standard deviation.

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