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Formulation And Characterization of Glyceryl Monooleate-Based Lyotropic Liquid Crystalline Gel of Meloxicam for Arthritis Therapy.

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ABSTRACT

This study aimed to formulate and evaluate a Meloxicam loaded lyotropic liquid crystalline gel for topical application. The topical route is preferable for arthritis treatment as it minimizes gastrointestinal toxicity associated with oral administration. Glyceryl monooleate was used as a biocompatible, bio-adhesive, penetration enhancer, and sustained-release agent. Six formulations of Meloxicam loaded lyotropic liquid crystalline gel (F1-F6) were prepared and evaluated for appearance, pH, Melting point, drug content, *in vitro* drug release. Pre-formulation studies, including IR spectroscopy, confirmed drug-polymer compatibility without significant chemical changes. *In vitro* release studies demonstrated sustained drug release over 12 hours, indicating that the formulated lyotropic liquid crystalline gel effectively penetrates the skin and enters systemic circulation. From the results we can be concluded that the lyotropic liquid crystal system provides a novel material for the preparation of topical drug delivery system for the poorly water-soluble drug meloxicam. These results suggest the feasibility of the topical gel formulation of meloxicam loaded lyotropic liquid crystalline gel.

Keywords: Lyotropic Liquid crystalline gel, Meloxicam, Topical, *In vitro* drug release.

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INTRODUCTION

Arthritis is a condition causing joint pain, stiffness, and inflammation. Common types include Osteoarthritis (OA), Rheumatoid Arthritis (RA), Gout, Psoriatic Arthritis, and Ankylosing Spondylitis. Joint pain, swelling, and reduced mobility are the common symptoms. Risk factors include aging, genetics, obesity, injuries, and autoimmune disorders. Diagnosis involves physical exams, blood tests, and imaging (X-rays, MRI). Treatment includes medications, physical therapy, lifestyle changes, and, in severe cases, surgery.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the treatment of pain and inflammation associated with conditions like osteoarthritis, rheumatoid [1] arthritis, and other inflammatory disorders. However, like many poorly soluble drugs, meloxicam faces challenges related to low bioavailability due to its poor solubility in water. In an attempt to overcome these limitations and enhance its therapeutic efficacy, the incorporation of meloxicam into lyotropic liquid crystal systems has been explored.

GIT irritation is a significant constraint associated with the use of nonsteroidal anti-inflammatory medications (NSAIDs). To avoid GIT irritation and other systemic side effects, there is growing interest in developing formulations that deliver the medicine directly to the site of action as topical gels [2]. The liquid crystal phase has emerged as a new material for the development of topical medication delivery systems. Lyotropic liquid crystalline gels, often referred to simply as lyotropic gels, are fascinating materials with a range of applications in various fields such as pharmaceuticals, cosmetics, and materials science.

The rationale for utilizing lyotropic liquid crystalline gels [3] lies in their unique combination of structural versatility, high water content, thermodynamic stability, tunable mechanical properties, and suitability for various applications such as drug delivery, cosmetics, and materials science. Their diverse properties make them valuable materials with promising potential in numerous fields. In present study the attempt is made to prepare Meloxicam (MLX) loaded lyotropic liquid crystalline gel using glycerol monooleate.

Lyotropic liquid crystals [4] are self-assembled, ordered structures formed by the interaction of surfactants, lipids, and solvents (typically water or oils) under specific conditions of temperature, concentration, and pressure. They are versatile systems that can form different mesophases, such as micellar, hexagonal, cubic, and lamellar phases, depending on the components and the external environment.

These systems have unique properties that make them suitable for drug delivery, including:

Enhanced drug solubility: Lyotropic liquid crystals (LLCs) can encapsulate hydrophobic drugs, improving their solubility in aqueous environments.

Controlled release: The structured nature of LLCs can provide a sustained release profile for drugs, making them effective for long-term therapeutic applications.

Improved bio-availability: By improving solubility and enabling more efficient drug absorption, LLCs can enhance the bioavailability of poorly water-soluble drugs like meloxicam.

The incorporation of meloxicam into LLCs typically involves selecting appropriate surfactants and co-surfactants to form a stable mesophase that can efficiently encapsulate meloxicam molecules. Surfactants like phospholipids, glycolipids, or polysorbates are commonly used to create these systems, often in combination with water, oils, and other excipients

MATERIALS AND METHODS

Materials

Drug Meloxicam was obtained as a gift sample from Zydus Lifesciences Ltd, Ahmedabad. Pluronic F–127 (PF 127) was issued from Sigma Aldrich. Glyceryl Monooleate (GMO) - 50, EP/N, solvents/chemicals used were obtained from Prince chemicals Co. Bangalore.

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Experimental

Preparation of MLX loaded liquid crystalline gel [5]

The lipid base (GMO) is melted at 37 ^{0}C and after complete melting of base the drug is added with constant stirring. At the same time the distilled water will be heated in another beaker and surfactant (PF 127) is added to the aqueous base with constant stirring on a magnetic stirrer. Upon complete dissolution of the aqueous phase was added drop by drop to the lipid phase with constant stirring until a gel mass is formed.

Table 1: Composition of meloxicam loaded liquid crystalline gel.

Sl No	Ingredients	Formulation code					
		F1	F2	F3	F4	F5	F6
1	Drug	100mg	100mg	100mg	100mg	100mg	100mg
2	GMO: Water (%)	10:90	20:80	30:70	40:60	50:50	60:40
3	F127 (mg)	200	400	600	800	1000	1200

Evaluation of MLX lyotropic liquid crystalline gel

Pre-formulation studies [6]: Pre-formulation testing is the initial step in developing dosage forms for a medicine. It is described as the study of the physical and chemical properties of a pharmacological substance both alone and in combination with excipients. Providing data that will assist the formulator in creating stable, bioavailable dosage forms that can be mass produced is the ultimate objective of pre-formulation testing.

Physical Appearance: All the batches of MLX loaded liquid crystalline gel formulations were observed for appearance, color, and consistency.

pH: The pH of the dispersion was determined using a digital pH meter. This method was repeated three times.

Melting Point Determination [7]: Melting point of the MLX was determined by capillary fusion method; one sided closed capillary filled with drug and put into the Melting Point Apparatus.

Identification of Meloxicam (MLX): Identification of MLX was carried out by Infra-Red Absorption spectrophotometry.

Compatibility Studies [8]: A successful formulation of a stable and effective solid dosage form is dependent on the careful selection of excipients used to facilitate administration, enhance consistent drug release and bioavailability, and protect the medication against degradation. Compatibility studies are critical when using new excipients that have not previously been used in formulations containing the active ingredient.

Compatibility of the MLX with polymer, was established by infrared absorption spectral analysis (IR). Any changes in chemical composition of the drug after combining it with the excipients were investigated with I.R. spectral analysis.

Drug Content Estimation

Preparation of Standard Calibration Curve of Meloxicam [9]: 100 mg of MLX was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with Phosphate buffer pH 6.8 to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with Phosphate buffer, pH 6.8 to get 1 to 12µg/ml of MLX. The absorbances of the solution were measured against Phosphate buffer as blank at 365 nm using UV spectrophotometer respectively. The standard calibration curve was created by plotting the absorbance readings against the concentration (µg/ml).

Drug Content [10]: 0.50 gm. MLX, liquid crystalline gel was weighed accurately. It was added in 100 ml volumetric flask containing 100 ml of Phosphate buffer 6.8. Resultant solution was kept forsonication for 30 min. for complete solubility of drug, and compared with standard absorbance at same wavelength and concentration. Thus % Assay was calculated this procedure was carried out in Triplicate.

***In-vitro* drug release [11]:** The *in vitro* drug release of the MLX loaded lyotropic liquid crystalline gel was performed to investigate the amount of drug released from a gel shown in Fig 4. Dialysis membrane was used as diffusion membrane. Membrane was soaked in phosphate buffer 6.8 for 2 hours before subjecting to diffusion study. The membrane was placed between a glass chamber's two cell halves. A clamp held the two chambers together. There were 25 milliliters of phosphate buffer in the receiver/receptor compartment. A uniform layer of 0.5 grams of formulation was applied to the membrane in the upper donor compartment. A circulating water bath was used to keep the receptor phase (phosphate buffer) at 37 °C while a magnetic stirrer was used to continually agitate it at 300 rpm. At specified intervals, 3 ml of the sample was removed, and new dissolving media was added. The samples collected from receiver compartment were analyzed for drug content using UV spectrometric method at 365 nm wavelength.

RESULTS AND DISCUSSION

Pre-formulation study

Melting Point

The melting point of MLX was found to be 240-242°C, which complied with IP standards thus indicating purity of obtained drug sample (Table 2).

Table 2: Melting point of drug by capillary method

Sample	Melting point (Practical)	Melting point (Theoretical)
Meloxicam	240-242°C	241°C

Compatibility study

Infrared spectroscopy of pure Meloxicam and physical mixture of drug and polymer were carried out for the identification of the drug and to confirm the compatibility of drug and polymer (Table3, Fig 1)

Table 3: Interpretation of IR Spectrum data

IR Spectrum	Peaks (cm^{-1})	Groups	Stretching / Deformation
MLX	3289.54	N-H (primary amine)	Stretching
	1619.86	C=O (aromatic ketone)	Stretching
	1551.90	C=N (thiazole ring)	Stretching
Physical mixture of MLX and Polymer	3285.65	N-H (primary amine)	Stretching
	1615.97	C=O (aromatic ketone)	Stretching
	1551.90	C=N (thiazole ring)	Stretching
	2924.54	C-H(aromatic)	Stretching

The principal peaks correspond to the structural features of Meloxicam are found due to presence of N-H stretching of primary amine at 3289.54 cm^{-1} the peaks at 3500 to 3200 cm^{-1} and 1619.86 cm^{-1} indicated presence of C=O stretching. Peak of 1551.90 cm^{-1} confirms the presence of C=N in thiazole ring [12].

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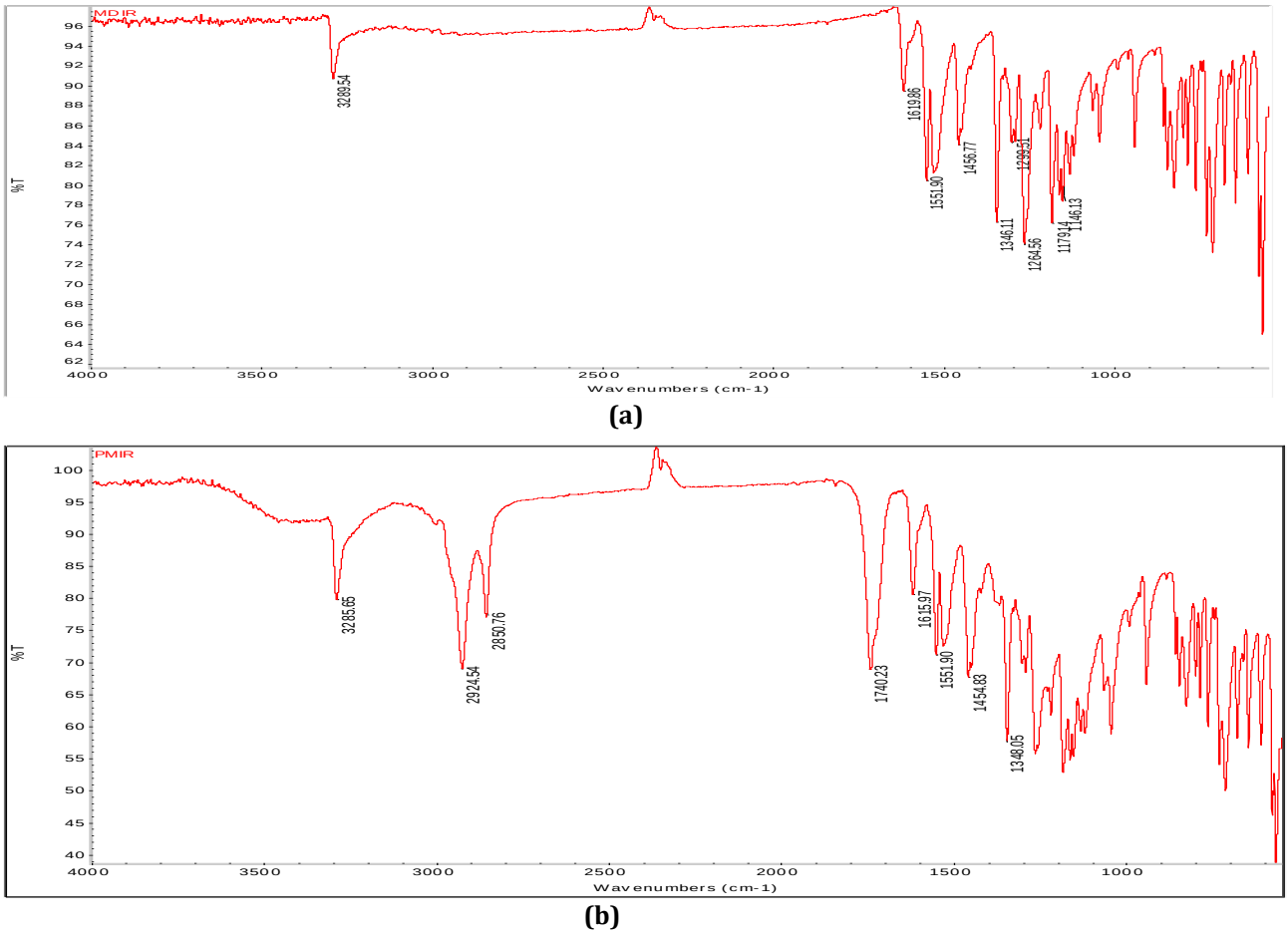

Figure 1: FT-IR spectrum of (a) Meloxicam (b) physical mixture of drug with polymer.

From the FTIR spectra, it is observed that the peak at 3285.65 cm^{-1} confirms the presence of N-H stretching and peak at 1615.97cm^{-1}confirm the presence of C=O stretching and the peak of 1551.90 cm^{-1} confirms the presence of C=N in thiazole ring. The principal peaks correspond to the structure features of Meloxicam are found due to the presence of N-H stretching of primary amine at 3289.54 cm^{-1} the peaks at 3500 to 3200 cm^{-1}

Characterization of MLX lyotropic liquid crystalline gel

Results of Physicochemical Properties of Meloxicam loaded Liquid crystalline gel is shown in Table 4.

Table 4: Physicochemical Properties of Meloxicam loaded Liquid crystalline gel

Formulation	Appearance	pH	Drug Content (%)
F1	Transparent, less viscous	6.6	65.58
F2	Slight phase separation	6.8	70.21
F3	Translucent, smooth, viscous	7.0	76.50
F4	Translucent, smooth, viscous	6.9	83.32
F5	Translucent, smooth, viscous	7.1	86.78
F6	Translucent, smooth, viscous	7.2	89.12

The Meloxicam loaded lyotropic liquid crystalline gel formulations were observed under dark background for its physical appearance. The observations for various formulations showed yellow viscous preparation with smooth,homogenous and consistent appearance [13].

Using a digital pH meter, the formulations' pH was measured and confirmed to be within the range needed for topical application.

Drug Content Estimation

Meloxicam content in each formulation was determined and reported in Table 4. The drug content from 65.58 % to 89.12% was obtained in the method employed in the study. It was observed that the dug content was increased by increasing polymer concentration [14].

***In-vitro* release studies**

In-vitro release studies were carried out. Cumulative % drug release after 12 hrs was 94.92%, 81.84%, 90.34%, 84.43%, 89.85% and 86.34% for F1, F2, F3, F4, F5 and F6 respectively (Fig 2). As the amount of polymer added to each formulation increased, it was found that the drug release from the formulations reduced [15].

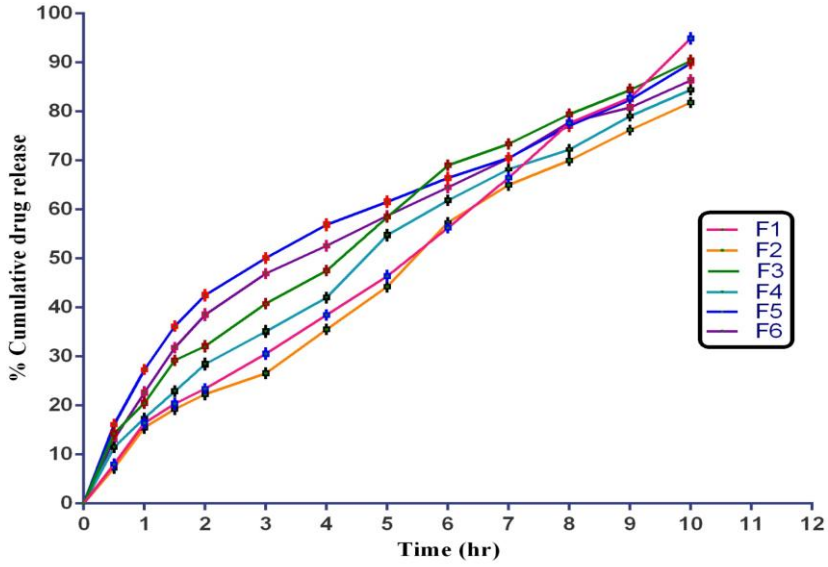

Figure 2: *In-vitro* release profile of meloxicam loaded liquid crystalline gel.

CONCLUSION

From the results we can conclude that the lyotropic liquid system provides a novel material for the preparation of topical drug delivery system for the poorly water-soluble drug Meloxicam. These results suggest the feasibility of the topical gel formulation of meloxicam loaded lyotropic liquid crystalline gel.

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