

# Enhanced Solubility of Meloxicam with Sodium Benzoate Hydrotrope: Ecofriendly Approach for Improved Topical Drug Delivery

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## ABSTRACT

**Background:** Hydrotropic solid dispersion has been reported as a potential process to improve the poor solubility of drugs using conventional hydrotropes. The presented investigation has described a water-soluble hydrotropic solid dispersion system for Meloxicam (MX) using sodium benzoate hydrotrope to enhance the poor solubility of Meloxicam and to improve topical delivery. Thus, solid dispersion was prepared, characterized, and converted into HSD-Meloxicam gel. The prepared gel was further characterized for *in vitro* performance. **Material and Methods:** Solid dispersion was prepared by a solvent evaporation method using sodium benzoate in 1:4 ratios. The prepared systems were characterized for *in-vitro* release and drug content. Accordingly, rate-controlling polymer and drug penetration enhancers were selected and formulated into hydrogel bases. The prepared gel was evaluated for performance parameters like drug content, pH, viscosity, spreadability, drug release kinetics, diffusion study, accelerated stability studies, and viscosity parameters. **Results:** HSD-Meloxicam gel containing carbopol-934 (20%w/w) has appeared a 99% release of the drug over 60 min of time duration. The prepared gel has clarity and is homogeneous in appearance. Similarly, *in-vitro* dissolution studies showed the prepared HSD Meloxicam gel's better release and rheological properties. The drug content of gel was found as 96% with improved topical delivery.

**Keywords:** Hydrotropes, Hydrotropic solid dispersion, Solubility, Dissolution, Topical gel, Stability studies.

## INTRODUCTION

Poor aqueous solubility hinders drug design and formulation since it causes delivery concerns such as erratic absorption and low bioavailability. This is particularly applicable to BCS (Biopharmaceutics Classification System) Class II drugs, compounds with low aqueous solubility and high permeability. The desired formulation for such drugs is always the primary concern. Thus, numerous approaches have been utilized to solve such compounds' solubility issues. Methods used for solubility enhancement enclosed solid dispersion, co-solvency, salt formation, co-crystal formation, and cyclodextrin complex formation. The reported techniques

have employed large amounts of organic solvents.<sup>1-3</sup> The significant drawbacks of organic solvents in the solubilization of the drugs include possible variations due to the volatility. Most of the organic solvents even possess significant toxicity and are pricey. Using hydrotropes, a water-soluble compound, in enhancing the solubility of drugs, especially NSAIDs in the aqueous medium, has recently received much interest in pharmaceutical industries. The term "Hydrotrope" was coined in 1916 by Neuberg. According to Neuberg, aqueous solutions of certain organic salts possessed the power to increase the solubility of water-

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insoluble substances in water. These organic salts are known as hydrotropes. The term 'Hydrotrophy' has later been introduced to describe the action of a hydrotrope. Hydrotrophy is defined as a solubilization phenomenon whereby the excessive amount of other solute increases the water solubility of the substance to be dissolved.<sup>4-6</sup> Unlike organic solvents, these are non-volatile, non-inflammable, non-toxic, inexpensive, and ecofriendly. The most widely used hydrotropes include urea, sodium benzoate, sodium citrate, sodium acetate, nicotinamide, and caffeine etc. For reference, several studies by Maheshwari *et al.* have reported hydrotropes' utility (sodium benzoate, urea, nicotinamide, sodium citrate, and sodium acetate) in enhancing the solubility and analyzing numerous poorly soluble drugs.<sup>7-10</sup> Systemic delivery of drugs via transdermal routes has generated considerable interest during the last decade. Transdermal drug delivery systems deliver drugs through the skin into the systemic circulation at a predetermined rate, thereby avoiding metabolism in the GI tract and liver. Therefore, the number of active ingredients required for transdermal delivery can be significantly less than that for oral systems. This system provides constant blood levels for 1 to 7 days and increases patient compliance. The efficacy of non-steroidal anti-inflammatory drugs is well known for treating inflammatory disorders such as muscle pain, osteoarthritis, and rheumatoid arthritis.<sup>11-14</sup> Meloxicam, an Oxicam derivative of non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties, is chemically 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide (Figure 1). Meloxicam acts by inhibiting the prostaglandin synthetase (cyclooxygenase 1 and 2) and reduces the levels of prostaglandins; thereby, inflammation that leads to pain, tenderness, and swelling gets suppressed. The drug is officially approved for treating inflammations associated with arthritis.<sup>15-17</sup> It is a class II BCS drug with poor aqueous solubility. The oral

route is mostly preferred for Meloxicam administration and causes many side effects in GIT like nausea, pain, vomiting, and diarrhea and it is reported that the topical administration of the drugs may overcome these side effects. Thus, meloxicam transdermal route as an alternative route was found to be a suitable route to avoid GIT side effects and improve patient compliance. The skin is the primary barrier for the transdermal delivery of various therapeutic molecules and is of potential relevance for topical dosage forms, especially for local treatments that require high drug concentrations in the target tissue. However, the major limitation of this route is difficulty of permeation of drug through the skin and is promoted by percutaneous administration of number of drug is promoted by suitable permeation enhancer.<sup>18-20</sup> The suitable characteristics of permeation enhancers should be inert, non-toxic, non-allergic, non-irritating, and must be compatible with other excipient.<sup>21-25</sup>

Thus, the prime goal of this study is to develop the drug delivery system for Meloxicam with improved solubility to improve the transdermal drug delivery. Formerly no such type of study has been reported. Thus, due to the low molecular weight (351.4g/mol) of Meloxicam and its potent nature, Meloxicam was selected for the study. The solubility of the Meloxicam was improved by using a 2M sodium benzoate hydrotropic solution. Therefore, hydrotropic solid dispersion was developed and characterized for *in-vitro* parameters to improve topical drug delivery.

Similarly, the topical gel was prepared by incorporating the prepared hydrotropic solid dispersion using Carbopol 940 (20% w/w) as a gelling agent and propylene glycol as a penetration enhancer. Using hydrotropes in the topical gel has improved the liposomal membrane permeability and induced the swelling action by showing adequate solubilizing action and increasing the microviscosity of the gel in the water phase. The prepared gel was further characterized for *in-vitro* performance parameters.

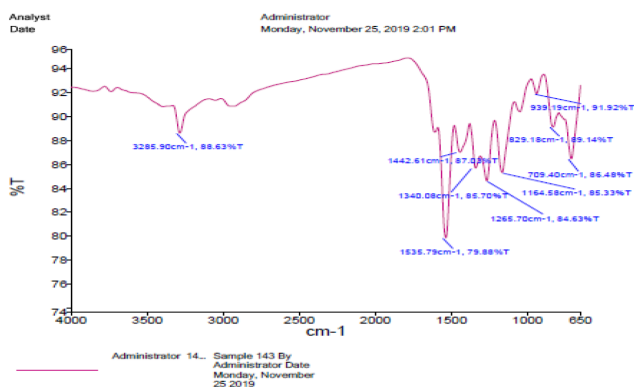
### Drug Profile of Meloxicam and Sodium benzoate.<sup>26-33</sup>

Detailed description of Meloxicam and sodium benzoate hydrotrope is presented in Table 1 given below:

## MATERIALS AND METHODS

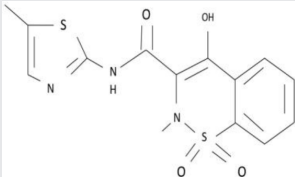
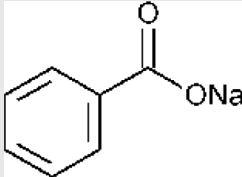
### Materials

Meloxicam was supplied by Akums Drugs and Pharmaceutical Ltd Haridwar as a gift sample. Sodium benzoate and phenolphthalein were purchased from CDH. All chemicals and solvents used in the study were of analytical grade.



**Figure 1: FTIR spectra of Meloxicam and sodium benzoate.**

**Table 1: Showing the profile of meloxicam and sodium benzoate hydrotrope.**

Generic name	Meloxicam	Sodium Benzoate
IUPAC Name	4-Hydroxy-2-methyl-N-(5-Methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide	Sodium benzoate
Molecular formula	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	C <sub>7</sub> H <sub>5</sub> NaO <sub>2</sub>
Molecular weight	351.4g/mol	144.1 g/mol
Structure		
Physical state	Crystal from ethylene chloride, pastel yellow solid	It occurs as white granules with a colorless, odorless and sweetish, astringent taste. It seems to occur as dry powder, liquid, and as pellets large crystals
Functional category	Anti-inflammatory, analgesic.	Antifungal agents, preservatives in food and pharmaceutical preparation.
pKa	4.08	-
Solubility	Higher soluble in strong acids and bases, very slightly soluble in methanol, Practically insoluble in water i.e., 22 mg/ml (25°C)	Sparingly soluble in ethanol but freely soluble in water.
Volume of distribution	The volume of distribution of Meloxicam around 10-15L as binding to albumin. Through the highly perfused tissue, kidney after the estimation around 40%-50% as it show its concentration in synovial fluid, plasma as well as placenta when given orally given.	-
Protein binding	The protein- bound of Meloxicam is about 99.4% in essence to albumin.	-
Oral bioavailability	89%	-
Half-life	As compare to NSAIDs, the half-life of meloxicam around 20 hr. Without requirement of slow-release formulations, therefore it is dosed.	-
Pharmacodynamics	As treatment of arthritis and osteoarthritis thus, Meloxicam has been used, and also used to treat dental or post-surgical pain and neuropathic pain as well.	-
Mechanism of action	Meloxicam decreased synthesis of prostaglandins, (cyclooxygenase 1 and 2) enzymes which is a mediator of painful inflammatory symptoms. It inhibits COX-2 and COX-1 enzymes, causing various hindrances, i.e., gastrointestinal irritation.	-
Pharmacokinetic Parameter Absorption	For oral capsule, after a dose was 89%, it exhibit absolute bioavailability of Meloxicam. After single dose where the C <sub>max</sub> reached up to 5-6 hr while on the other hand, the C <sub>max</sub> becomes doubled in the fasting state.	-
Distribution	It is highly perfused through the tissue i.e., liver, placenta and kidney, due to its high binding to albumin in which the volume of distribution about 10-15L. When given through oral route thus the concentration of meloxicam exhibit 40-50%.	-
Metabolism	The enzyme responsible for the complete metabolism of meloxicam is CYP2C9 and also CYP3A4 as a minor enzyme. As from Cytochrome enzyme oxidation, it is metabolized to 5'-carboxy Meloxicam from hepatic about 60% through the ingested dose of intermediate metabolites i.e., 5'-hydroxymethyl meloxicam where other two metabolites released by peroxidation.	-
Elimination	The metabolism of meloxicam is cleared through fecal and renal route however the dose eliminated is <0.25% unchanged form through the urine and about 1.6% is excreted through the feces.	-

## Instruments and Equipment

A Double-beam UV-Visible spectrophotometer model (UV-1700 PC) SHIMADZU (Japan) used the SHIMADZU UV probe data system to measure drug absorption. Ultrasonic device HICON was used for drug dissolution for solubility studies. Shimadzu-FTIR 8300 spectrophotometer was used to record the IR spectra of the drug and hydrotrope.

## Hydrotropic solubilization of Meloxicam in 2M sodium benzoate solution

The equilibrium solubility studies of Meloxicam were performed using a 2M molar sodium benzoate solution. A hydrotropic molar solution was taken in a vial, and the required number of drugs was added. A vial was kept in a water bath shaker and shaken for 12 hrs to obtain the saturated solution. The vial was allowed to equilibrate for 24 hr to attain equilibrium solubility. Thus, solubility enhancement of the drug was observed, and the solubility enhancement ratio was calculated as per the formula given below.

$$\text{Enhancement ratio} = \frac{\text{Solubility of drugs in hydrotropic solution}}{\text{Solubility of drugs in distilled water}}$$

## Compatibility study

A compatibility study of Meloxicam and sodium benzoate was performed by mixing drug and hydrotrope in the ratio of 1:1 in mortar-pestle, and pellets were pressed at 20 psi for 10 min on KBr-press. IR spectra were taken in Fourier transform infrared spectrophotometer (840, Shimadzu, Japan) at a wavenumber range of 4000-6000  $\text{cm}^{-1}$ .

## Preparation of hydrotropic solid dispersion and physical mixture

10 gr hydrotropic solid dispersion of Meloxicam and sodium benzoate in 1:4 was prepared. A Teflon-coated magnetic bead was used for continuous stirring. An accurately weighed amount of drug and hydrotrope was placed in a beaker containing the minimum amount of distilled water maintained at temperature 60-80°C. Continuous stirring was done at temperature 30-40°C until complete solubilization of the drug. Stirring was continued until semisolid mass was obtained. Then drying of mass was done in the oven at 40°C by placing the mass on the watch glass. Dried mass was triturated to convert into powdered mass in a mortar pestle. The dried powder was sieved through sieve no 100 and kept in a desiccator with blue silica gel for one week. Then prepared solid dispersion was stored in an appropriate air-tight container.<sup>34-40</sup>

Similarly, a physical mixture of Meloxicam and sodium benzoate was also prepared in ratio of 1:4. Intense trituration of drug and hydrotrope was performed for 10 min in mortar and pestle. Then, powder mass was sieved through sieve no. 100 and stored in a desiccator.

## Evaluation of prepared HSD

### Fourier transform infrared spectroscopy

FTIR spectra of the meloxicam (drug alone), HSD and PM were determined. 1–2 mg of meloxicam drug, prepared HSD and PM were mixed with potassium bromide and pellets were made and examined in a transmission mode over a wave number range of 4000 to 400  $\text{cm}^{-1}$ .

### Percent drug content

The drug contents and percentage yields of the SDs and PMs were determined. The hydrotropic solid dispersion and physical mixture equivalent to 10 g of drug was added in required volume of distilled water. The drug content was assayed by a UV spectrophotometer at 279 nm. Analysis was done in triplicate. Using the given below formula, percent drug content and yield was calculated:

$$\% \text{ Yield} = (a/b) \times 100$$

'a' = Practical weight of HSD obtained/PM obtained

'b' = Theoretical weight of HSD/PM

### In-vitro Dissolution Studies

The *in-vitro* dissolution study was performed for pure meloxicam, HSD, and PM.

USP XXIV (type II) dissolution apparatus was used for estimating the dissolution rate. 100mg of pure drug, HSD, and PM were dissolved in 500ml of distilled water maintained at  $37 \pm 0.5^\circ\text{C}$  at 50 rpm. 10 ml of sample solution was withdrawn at 10 mins of time interval and replaced with the same volume of distilled water to maintain the sink condition. Withdrawn samples were then analyzed in a UV spectrophotometer to determine the absorbances at 269 nm. The amount of drug dissolved was calculated by using the regression equation.

### Differential scanning calorimetry

For DSC thermograms, 4 mg of pure meloxicam, HSD equivalent to 4 mg, and PM were placed in an aluminum pan, sealed, and packed. DSC analysis was performed using a heating and cooling cycle from 40-4000 c at a constant rate of  $10^\circ\text{C}/\text{min}$ . Nitrogen gas at a 50 ml/min flow was purged to maintain an inert environment.

### X-ray Powder Diffraction Study

XRD spectra for the pure Meloxicam, HSD, and PM were collected with scans from  $2\theta$  values of 5 to  $60^\circ$  at 30 mA current and 30 kV voltages.

### Stability study

The prepared HSD was subjected to stability studies conducted for three months. Meloxicam HSD was stored at conditions  $25^\circ\text{C}/75\%\text{RH}$ ,  $40^\circ\text{C} /75\%\text{RH}$  and  $55^\circ\text{C}/75\% \text{RH}$ . Samples were collected after three months at each temperature condition, and drug content that remained in HSD was determined for analysis.

### Preparation of HSD Topical gel

HSD-Meloxicam gel was prepared by the dispersion method. The exact amount of carbopol 940 (20%), powdered HSD (30%), propylene glycol (10%), methyl parabens (0.1%) was dispersed in distilled water. Dispersion of carbopol 940 was allowed to stand for 24 hrs for complete swelling. Other ingredients were adequately added in dispersed carbopol with continuous stirring to acquire gel aspect. The required quantity of triethanolamine was added and neutralized with dispersed carbopol to maintain pH 5.0-5.5. Then, propylene glycol was added with the previous mixture and equilibrated for 24 hr at room temperature and stored at appropriate condition.<sup>41-43</sup>

### In-vitro Performance Study

The prepared HSD-Meloxicam gel was inspected visually for the color, homogeneity (appearance and presence of any aggregates), grittiness (presence of particles or grits), and syneresis (phase separation).

### Measurement of pH

With the aid of a digital pH meter, the pH of the gel was determined at room temperature. 2 gm quantity of gel was evaluated in 25 ml of distilled water, and pH was recorded.

### Viscosity

The viscosity of the prepared gel was determined using spindle no7 of Brookfield's viscometer. The spindle was dropped perpendicularly into the gel and rotated at 10, 20, 30, 40, 50, and 60 rpm. The corresponding dial reading was recorded at each subsequent rotation.

### Spreadability

The convenient glass plate method was employed for the spreadability study. About 0.5 g of the gel was spread on a marked circle of 2cm diameter of the first glass plate, and then a second glass plate was then pulled over the first glass plate. A weight of about half a kilogram was

placed on the upper glass plate and left at rest for 5 min. The diameter of the circle acquired by the gel was noted and the given formula calculated spreadability:

$$\text{Spreadability} = \frac{(\text{weight} \times \text{Length})}{\text{Time}}$$

### In-vitro Drug Content Study

For confirming the uniform formulation of the gel, drug content was determined. 1gm of gel was accurately weighed and dissolved in 100 ml of calibrated phosphate buffer of pH. 7.4. Appropriate dilutions with the same phosphate buffer were made by transferring the solution in a volumetric flask and stirred for 24 hrs on a magnetic stirrer. After subsequent filtration of solution with  $0.45 \mu\text{m}$  Whatman filter paper, the drug content of gel was determined spectrophotometrically at 269 nm.<sup>44-45,39-40,42,46,47</sup>

### In-vitro Drug Release Study

For permeation studies, a modified Franz diffusion cell was incorporated. Cellophane membrane was (no. 10, pore size 2.4 nm) soaked in phosphate buffer of pH 7.4 for 24 hr before use. Cellophane membrane was placed in between the donor and receptor compartment. Accurately weighed, 100mg of the gel was transferred to the donor compartment, and 25 ml of distilled water was filled in the receptor compartment. The cell was agitated on a magnetic stirrer at 50 rpm, and the temperature was maintained at  $37 \pm 1^\circ\text{C}$ . Aliquots were withdrawn at a specific time interval and replaced with an equal volume of fresh phosphate buffer pH 7.4. The samples were diluted suitably, and required absorbances were measured at 269 nm.<sup>48-50</sup>

### Accelerated stability studies of topical Gel

The accelerated stability studies were conducted as per ICH guidelines for 12 weeks. The formulations were stored in hot air oven at  $37 \pm 2^\circ\text{C}$ ,  $45 \pm 2^\circ\text{C}$ , and  $60 \pm 2^\circ\text{C}$ . A sample content was analyzed spectrophotometrically at 269 nm after every two weeks. Changes in physical appearance, pH, consistency, and gel precipitation were observed.<sup>51-53</sup>

### Drug Release Kinetic Study

The kinetics of drug release from the gel was assessed through various kinetic models. Three kinetic models, zero-order (1), first-order (2), and Higuchi square root models (3), were applied to the obtained drug release data.

$$Q = K_0 t \quad [1]$$

Where  $Q$  is the amount of drug release at time  $t$ ,  $K_0$  is the zero-order rate constant expressed in units of concentration/time, and  $t$  is the time. Consider

$$\log Q = \log Q_0 - \frac{K_1 t}{2.303} \quad [2]$$

Where  $K_1$  is the first-order constant, as well as  $C_0$ , indicated the initial concentration of the drug. Consider,

$$Q = K_H t^{1/2} \quad [3]$$

Where  $K_H$  is the constant reflects the design variables of the system. The mechanism of drug release data was fitted in the Korsmeyer-Peppas model as follows:

$$\frac{M_t}{M_\infty} = K t^n \quad [4]$$

Where  $K$  represented the release rate constant included structural and geometric characteristics of the tablet,  $M_t/M_\infty$  represented the fraction of drug released at time  $t$ , and  $n$  has indicated the release exponent. The  $n$  value, i.e., diffusion exponent, was then used to characterize different release mechanisms.

## RESULTS AND DISCUSSION

### Equilibrium Solubility Determination

The solubility of Meloxicam was significantly improved in screened hydrotropic solutions, with the highest increment in the solubility in the 2M sodium benzoate solution. Table 1 shows the obtained solubility of Meloxicam in different molar solutions of hydrotropes.

### Compability Study of Meloxicam and Sodium Benzoate for Preparation of Solid Dispersion

In a compatibility study of Meloxicam and sodium benzoate using FTIR, no considerable change in the peak of FTIR spectra was observed. Thus, the selected hydrotrope was found to be compatible with the drug. Figure 1 is shows the compatibility spectra of the drug and hydrotrope.

### Characterization of prepared HSD

#### Fourier transform infrared spectroscopy

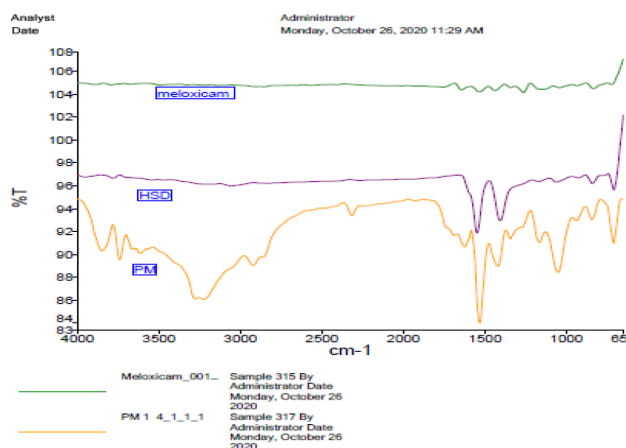
Pure Meloxicam, PM, and HSD spectra were recorded in FTIR study. PM and HSD showed the same peaks compared to pure meloxicam as shown in Figure 2. Thus, no interaction between the drug and the hydrotropic agent was reported.

### Percent Yield

The percentage yield was calculated for prepared HSD. The outcome showed significantly increased yield with

**Table 2: Showing the preliminary solubility study of Meloxicam drug.**

Drug (mg)	Solvent system	Temperature (°C)	Solubility enhancement ratio
Meloxicam	Distilled water	25°C	-
Meloxicam	2M Sodium benzoate	25°C	56.6
Meloxicam	2M Sodium salicylate	25°C	42.01
Meloxicam	2M Sodium acetate	25°C	35.81



**Figure 2: Combined FTIR spectra of pure Meloxicam, PM and HSD.**

**Table 3: In-vitro drug release of Meloxicam.**

Time(min)	Meloxicam	PM (1:4)	HSD (1:4)
0	0	0	0
10	12.18	17.24	25.02
20	18.48	25.42	34.32
30	20.96	36.84	55.42
40	24.02	48.16	66.74
50	26.5	55.16	82.26
60	28.34	58.26	90.58

increased polymer concentration up to 1:4 ratio. It showed more than 98.84 % percentage yield for HSD.

### In-vitro Percent Drug Release

The percent drug dissolution data of prepared HSD is shown in Table 2 and Figures 3 and 4. The percentage drug dissolution of HSD was 90.58 over 60 mins of study whereas 28.34 % and 58.26% were obtained for pure drug and PM respectively. Hence, the dissolution rate of Meloxicam was improved significantly in the presence of sodium benzoate.

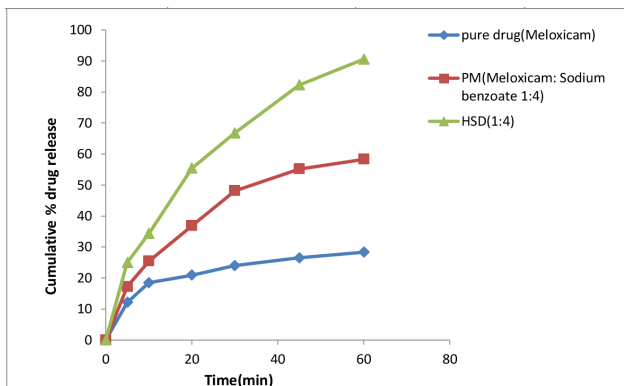


Figure 3: Graph showing drug dissolution of Meloxicam, PM and HSD.

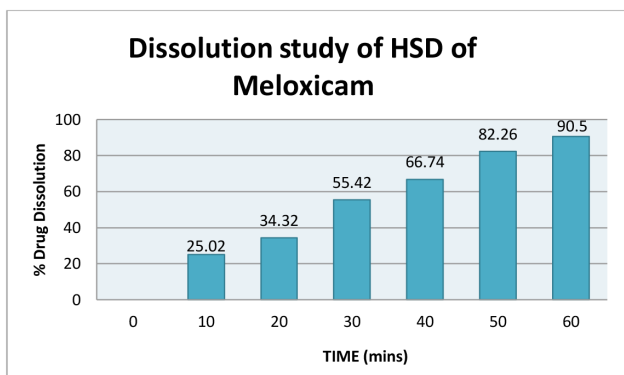


Figure 4: Graphical representation of *in-vitro* dissolution of HSD of Meloxicam.

**X-ray Diffraction Study**

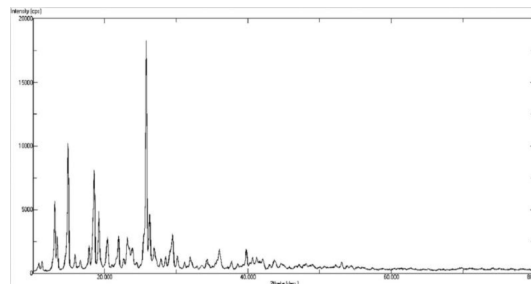
In the XRD study, the obtained diffraction spectra of Meloxicam HSD and PM showed the same intense and sharp peaks at 2θ. The XRD peaks were comparable and no chemical interaction was reported between drugs and hydrotropes. This, confirmed the crystalline nature of prepared hydrotropic solid dispersion, as shown in Figure 5.

**DSC**

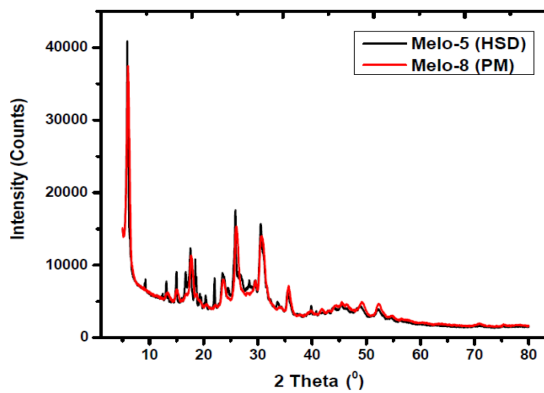
DSC study showed a high-intensity endothermic peak at 252°C, which was equivalent to the melting point of Meloxicam. This endothermic peak showed the crystalline nature of the drug. An endothermic peak at 400°C has indicated the melting point of sodium benzoate hydrotrope and confirmed its amorphous nature, Figure 6 Thus, it was proven that the crystallinity of Meloxicam was improved in the molecular dispersion of sodium benzoate.

**Stability study**

Table 4 shows the outcomes of stability data. No instability data were reported for prepared HSD

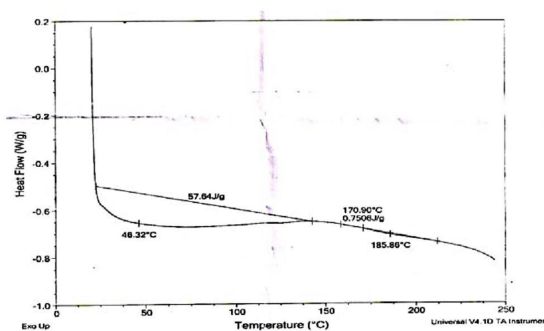


(a)

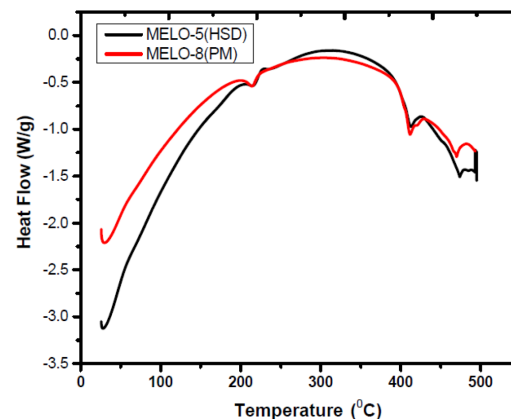


(b)

Figure 5: XRD spectra of (a) Meloxicam drug (b) PM and HSD of Meloxicam.



(a)



(b)

Figure 6: DSC thermogram (a) Meloxicam drug (b) PM and HSD of Meloxicam.

**Table 4: Data of stability study of HSD of Meloxicam (n=3).**

Sl. No.	Stability testing condition	Percent drug content
1.	Room temperature, 25°C/75% RH	98.47±0.01
2.	40°C/75%RH	98.34±1.02
3.	55°C/75% RH	98.11±2.13

**Table 5: Spreadability values for the formulation.**

Sl. No	Formulation	Spreadability (g.cm/sec)
1.	HSD Melo-G	8.35

**Table 6: The viscosity of the prepared gel.**

Sl. No.	Formulation	2 RPM	4 RPM	10 RPM	20 RPM
1.	HSD Melo-G	16000 cps	14300 cps	11500 cps	6100 cps

confirmed by drug content determination. Thus, Meloxicam HSD presented excellent stability.

## RESULTS

### Physical Evaluation

The prepared gel formulations clearly showed good homogeneity with the absence of lumps.

### Spreadability

The spreadability of the prepared gel was calculated and compared with a standard preparation. Table 5 shows the values of calculated spreadability.

### Measurement of pH

The pH of HSD Meloxicam gel was found in the range of 4.65 to 6 which lies in the normal pH range of skin.

### Viscosity

Table 6 shows the viscosity of prepared gel measured at 2, 4, 10, and 20 rpm. Viscosities were proportional to the concentration of the gelling agent.

### Drug Content

The drug contents of the prepared gels were found to be in the range of  $95.20 \pm 1.265$ , indicating high drug content uniformity showing in Table 7.

### Drug release kinetic study

Different mathematical models were used to describe the kinetics of Meloxicam topical gel. The release exponent ( $n$ ) values and the regression values of zero-order, first-order, and Higuchi release models for

**Table 7: Drug content of Prepared Gel.**

Formulation	Drug Content $\pm$ S.D. (%)
HSD Melo-G	$95.20 \pm 1.265$

**Table 8: Drug release kinetic study of Meloxicam topical gel.**

Formulation	Zero-order	First-order Correlation coefficient ((n) R <sup>2</sup> )	Higuchi model	Korsmeyer-Peppas model
HSD Melo-G	0.883	0.602	0.987	1.322

**Table 9: Accelerated Stability Study of Topical Gels of Meloxicam.**

Time (days)	Percentage of drug retained (log value)			
	RT	37±1° °C	45± 1° °C	60±1° °C
00	100.00(2.000)	100.00(2.000)	100.00(2.000)	100.00(2.000)
07	96.23(1.997)	96.52(1.997)	96.62(1.997)	96.61(1.998)
14	96.11(1.996)	96.21(1.996)	96.30(1.995)	96.35(1.995)
21	97.21(1.996)	97.25(1.995)	97.27(1.995)	97.30(1.995)
28	95.32(1.995)	95.32(1.995)	95.39(1.994)	95.38(1.994)
35	95.43(1.994)	95.45(1.994)	95.46(1.993)	95.50(1.993)
42	94.52(1.993)	94.52(1.993)	94.55(1.992)	94.56(1.992)
49	94.60(1.991)	94.63(1.992)	94.65(1.990)	94.55(1.991)

formulations are represented in Table 8. As indicated by their highest regression values, the Higuchi kinetic plot was linear, and the correlation coefficient value obtained ( $R^2$ ) was 0.602.

### Accelerated study

As per ICH guidelines, accelerated stability studies were conducted for seven weeks. The prepared meloxicam gel was stable at varying temperature conditions, and the results are given in Table 9.

### In-vitro drug diffusion /Permeation study

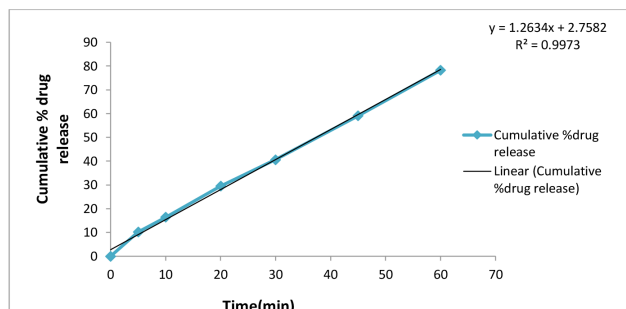
#### Cellophane membrane

The diffusion ability of prepared gel was evaluated through cellophane diffusion model using water as a diffusion medium. The study was conducted for 60 min and the cumulative percent drug diffused was calculated and presented in Table 10. The gel has shown an excellent release profile due to increased concentration of gelling agents that decreased drug release due to high viscosity showing in Figure 7.



**Table 10: Drug release profile of prepared gel.**

Sl. No.	Time (min)	Cumulative % drug diffused
1.	0	0
2.	5	10.24
3.	10	16.44
4.	20	29.48
5.	30	40.62
6.	45	59.09
7.	60	78.22

**Figure 7: In-vitro drug diffusion Study of Meloxicam gel.**

## RESULTS AND DISCUSSION

The initial solubility study of Meloxicam in molar solutions of different hydrotropes has shown a significant enhancement in solubility with the highest increment in 2M hydrotropic solution of sodium benzoate. Hence, hydrotropic solid dispersion using sodium benzoate in 1:4 ratios was carried out using the solvent evaporation method and evaluated for in-vitro parameters. Similarly, a physical mixture of Meloxicam in a 1:4 ratio with sodium benzoate was also prepared for comparative study. No compatibility issues were reported in the FTIR study between Meloxicam and sodium benzoate. Similarly, DSC and XRD have shown the reduced crystallinity of the drug and improved solubility in the molecular dispersion of sodium benzoate. The drug release of Meloxicam was improved in hydrotropic solid dispersion over 60 mins compared to the physical mixture evidenced by the in-vitro drug dissolution study. The prepared solid dispersion has shown remarkable stability in varying temperature conditions during storage and was thus chosen for topical gel preparation using carbopol 934 as a gelling agent. In an *in-vitro* evaluation of topical gel, acceptable values of pH and spreadability were obtained. Drug release in the topical gel was improved, i.e., 78.22% over 60 mins of the study. The percent drug diffusion study showed better release of Meloxicam in the presence of sodium benzoate and maintained the complete solubility in the release medium. The drug release kinetic study

of Meloxicam has shown the liner plot for the Higuchi model with a 0.602 regression coefficient value. Thus, based on the findings of experimental work, hydrotrope has potential not only in solving the solubility issues but a promising vehicle for topical administration of poorly water-soluble drugs. Therefore, hydrotropy is a more sustainable and economical approach to developing the transdermal preparations of other hydrotrope solubilized poorly soluble drugs.

## CONCLUSION

The prepared HSD meloxicam topical gel showed better release and complete solubility in the release medium. It changed the barrier function by improving the permeability of meloxicam in stratum corneum in the presence of sodium benzoate hydrotrope and is recommended as the ideal carrier for the topical delivery of the other poorly soluble drug.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

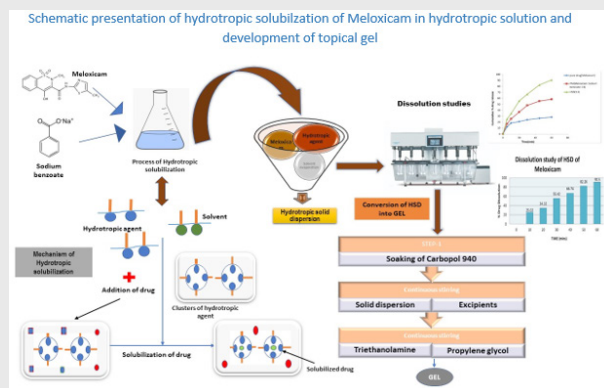
The authors declare no conflict of interest.

## REFERENCES

- Allawadi D, Singh N, Singh S, Arora S. Solid dispersions: A review on drug delivery system and solubility enhancement. *Int J Pharm Sci Res.* 2013;4(2):2094-105.
- Amravati V, Firoz S, Kishore D, Mouli YC. Formulation and evaluation of mefenamic acid tablets by using modified starch. *Asian J Pharm Sci Technol.* 2012;2(5):46-53.
- Argade PS, Magar DD, Saudagar RB. Solid Dispersion: Solubility Enhancement Technique for poorly water soluble Drugs. *Journal of Advanced Pharmaceutical Education Research.* 2013;3(1):427-39.
- Aseri A, Duggal D, Katewa J, Nayak A. Enhancement of solubility of poorly water soluble drug metronidazole by hydrotropy. *Asian J Pharm Res Dev.* 2013;1(2):98-102.
- Asija R, Kalariya N, Asija S, Arvind MT. Enhanced solubility study of sulphasalazine using different solubilization techniques. *Int Res J Pharm.* 2012;3(7):187-90.
- Dhandapani B, Murali SE, Susrutha N, Swetha R. Spectrophotometric estimation of meloxicam in bulk and its pharmaceutical formulations. *Int J Pharm Sci Res.* 2010;1(4):217-21.
- Beig A, Lindley D, Miller JM, Agbaria R, Dahan A. Hydrotropic solubilization of lipophilic drugs for oral delivery: The effects of urea and nicotinamide on carbamazepine solubility-permeability interplay. *Front Pharmacol.* 2016;7(3):379. doi: 10.3389/fphar.2016.00379, PMID 27826241.
- Bhoir S, Dhole S, Kulkarni N, Sangole P. Novel and validated spectrophotometric estimation of diacerein in bulk and capsule formulation using mixed hydrotropic solubilization approach. *Int J Pharm Sci.* 2012;4(5):501-4.

9. Choudhary NH, Kumbhar MS, Dighe DA, Mujgond PS. Solubility enhancement of escitalopram oxalate using hydrotrophy. *Int J Pharm Sci.* 2012;5(2):121-5.
10. Cid AG, Simonazzi A, Palma SD, Bermúdez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Ther Deliv.* 2019;10(6):363-82. doi: 10.4155/tde-2019-0007, PMID 31094298.
11. Dhapte V, Mehta P. Advances in hydrotropic solutions: An updated review. *Univers J Phys Math.* 2015;1(4):424-35. doi: 10.1016/j.spjpm.2015.12.006.
12. Jayakumar C, Raja C. A review on solubility enhancement using hydrotropic phenomena. *Int J Pharm Sci.* 2011;6(8):1-7.
13. Sintra TE, Abranches DO, Benfca J, Soares BP, Ventura SPM, Coutinho JAP. Cholinium-based ionic liquids as bioinspired hydrotropes to tackle solubility challenges in drug formulation. *Eur JPharmBiopharm.* 2021;164:86-92. doi: 10.1016/j.ejpb.2021.04.013.
14. Kadam PS, Pande SK, Vibhute MA. Exploration of mixed hydrotrophy strategy in formulation and development of etodolac injection. *Journal of Nanomedicine Research.* 2017;3(8):1-7.
15. Kamble R, Sharma S, Mehta P. Norfloxacin mixed solvency based solid dispersions: An *in-vitro* and *in-vivo* investigation. *J Taibah Univ Sci.* 2017;11(3):512-22. doi: 10.1016/j.jtusci.2016.11.003.
16. Kapadiya N, Singh I, Mehta K, Karwani K. Hydrotrophy: A promising tool for solubility enhancement: a review. *Int J Drug Dev Res.* 2012;3(4):26-33.
17. Kapse VN, Dharashive VM, Devne SRG. Effect of hydrotropes on solubility of drugs. *Int J Pharm Chem Sci.* 2016;5(2):48-52.
18. Kaushik A, Jat RK. Solubility enhancement of miconazole by formulation of hydrotropic solid dispersions. *J Drug Deliv Ther.* 2017;7(2):117-26.
19. Kaushik A, Jat RK. Solubility enhancement of fluconazole by formulation of hydrotropic solid dispersions. *Journal of Biomedicine in Pharmaceutics Research.* 2017;6(3):129-40.
20. Kim JY, Kim SW, Papp M, Park K, Pinal R. Hydrotropic solubilization of poorly water-soluble drugs. *J Pharm Sci.* 2010;99(9):3953-65. doi: 10.1002/jps.22241, PMID 20607808.
21. Kulkarni S, Goswami A. Research on application of hydrotrophy: A review. *International Journal of Science in Engineering Technology Research.* 2014;3(1):2617-9.
22. Li H, Ma L, Li X, Cui X, Yang WS, Shen S, *et al.* A simple and effective method to improve bioavailability of glimepiride by utilizing hydrotrophy technique. *Eur J Pharm Sci.* 2015;77(5):154-60. doi: 10.1016/j.ejps.2015.06.016, PMID 26093052.
23. Lipinski C. Poor aqueous solubility—an industry wide problem in drug delivery. *Am Pharm.* in review. 2005;5(5):82-5.
24. Madan JR, Kamate VJ, Awasthi R, Dua K. Formulation, characterization and *in-vitro* evaluation of fast dissolving tablets containing gliclazide hydrotropic solid dispersions. *Recent Pat Drug Deliv Formul.* 2017;11(2):147-54. doi: 10.2174/1872211311666170427100213, PMID 28460615.
25. Saffoon N, Uddin R, Huda NH, Sutradhar BS. Enhancement of oral bioavailability and solid dispersion: A review. *J Appl Pharm Sci.* 2011;1(3):13-20.
26. Sajid A, Choudhary V. Solubility enhancement methods with importance of hydrotrophy. *J Drug Deliv Ther.* 2012;2(8):96-101.
27. Shah M, Farooqui Z, Shah J, Shah N, Sheorey S. Solid dispersion- a way to enhance solubility of quetiapine fumarate. *Am J Pharm Technol Res.* 2013;6(8):732-48.
28. Sharma A, Jain CP. Solid dispersion: A promising technique to enhance solubility of poorly water. *Int J Drug Deliv.* 2011;3(5):149-70.
29. Sharma N, Singh S. Central composite designed ezetimibe solid dispersion for dissolution enhancement: Synthesis and *in vitro* evaluation. *Ther Deliv.* 2019;10(10):643-58. doi: 10.4155/tde-2019-0063, PMID 31702450.
30. Sharma S, Chauhan V, Khan MK. Formulation optimization of mouth dissolving tablets of meloxicam using mixed hydrotropic solubilization technique. *J Sci Innov Res.* 2015;4(8):76-82.
31. Shelke SP. Enhancement of solubility of mefenamic acid by hydrotrophy based solid dispersion. *Int J Sci Res Technol.* 2018;4(9):147-9.
32. Singh S, Singla YP, Arora S. Box-Behnken Design, Statistical, diagnostic and response surface analysis of nefopam hydrochloride Nano spheres using 35 Box Behnken design. *Int J Pharm Sci.* 2015;7(1):89-101.
33. Surwade KS, Saudagar RB. Solubility enhancement of azilsartan medoxomil using mixed hydrotrophy. *World J Pharm Sci.* 2015;4(4):1167-79.
34. Yadav B, Tanwar YS. Applications of solid dispersions. *J Chem Pharm Res.* 2015;7(9):965-97.
35. Yadav NK, Shukla T, Upmanyu N, Pandey SP, Khan MA. Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. *J Drug Delivery Ther.* 2018;8(5):481-8. doi: 10.22270/jddt.v8i5.1911.
36. Reddy MN, Murthy TK, Rajita K, Shankar DG. New spectrophotometric methods for the determination of meloxicam. *Indian J Pharm Sci.* 2003;65(7):655-8.
37. Neelam S, Garg A, Sonu B. Spectrophotometric method for estimation of some COX-2inhibitors in pure form and in pharmaceutical formulations. *Indian J Pharm Sci.* 2003;65(9):685-8.
38. Gates BJ, Nguyen TT, Setter SM, Davies NM. Meloxicam: A re-appraisal of pharmacokinetics, efficacy and safety. *Expert opinion in pharmacotherapy.* 2005;6(4):2117-40.
39. Jantharaprapap R, Stagni G. Effects of penetration enhancers on *in vitro* permeability of meloxicam gels. *Int J Pharm.* 2007;343(1-2):26-33. doi: 10.1016/j.ijpharm.2007.04.011, PMID 17531412.
40. Chang JS, Huang YB, Hou SS, Wang RJ, Wu PC, Tsai YH. Formulation optimization of meloxicam sodium gel using response surface methodology. *Int J Pharm.* 2007;338(1-2):48-54. doi: 10.1016/j.ijpharm.2007.01.033, PMID 17360134.
41. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. *Int J Pharm.* 2008;346(1-2):124-32. doi: 10.1016/j.ijpharm.2007.05.060, PMID 17651933.
42. Joshi MD, Patravale VB. Formulation and evaluation of Nanostructured lipid carrier (NLC) based gel of valdecoxib. *Drug Dev Ind Pharm.* 2006;32(8):911-8. doi: 10.1080/03639040600814676, PMID 16954103.
43. Lee PJ, Langer R, Shastri VP. Role of N-methyl pyrrolidone in the enhancement of aqueous phase transdermal transport. *J Pharm Sci.* 2005;94(4):912-7. doi: 10.1002/jps.20291, PMID 15736187.
44. Yogeshwar GV, Vandana B. Formulation of meloxicam gel for topical application: *In vitro* and *in vivo* evaluation. *Acta Pharm.* 2010;60(4):153-63.
45. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery, National review in drug discovery. *Nat Rev Drug Discov.* 2004;3(2):115-24. doi: 10.1038/nrd1304, PMID 15040576.
46. Sanghvi R, Narazaki R, Machatha SG, Yalkowsky SH. Solubility improvement of drugs using N-methyl pyrrolidone. *AAPS Pharm Sci Tech.* 2008;9(2):366-76. doi: 10.1208/s12249-008-9050-z.
47. Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev.* 2004;56(5):603-18. doi: 10.1016/j.addr.2003.10.025, PMID 15019749.
48. Kaur T, Gill B, Kumar S, Gupta GD. Mouth dissolving tablets: A novel approach to drug delivery: A review. *Int J Curr Pharm Res.* 2011;3(4):1-7.
49. Ibrahim N, Smail S, Hussein N, Abdullah T. Solubility enhancement of nimodipine using mixed hydrotropic solid dispersion technique. *Zanco J Med Sci.* 2020;24(3):386-94. doi: 10.15218/zjms.2020.046.
50. Godase CB, Babar AL, Gopal AB. A concise review on methods of solubility enhancement. *Int PharmSci.* 2020;11:109.
51. Marei HF, Arafat MF, Essa EA, El Maghraby GM. Lidocaine as eutectic forming drug for enhanced transdermal delivery of nonsteroidal anti-inflammatory drugs. *J Drug Deliv Sci Technol.* 2021;61. doi: 10.1016/j.jddst.2021.102338, PMID 102338.
52. Oliveira BED, Amorim OHJ, Lima LL, Rezende RA, Mestnik NC, Bagatin E, Leonardi GR. 5-Fluorouracil, innovative drug delivery systems to enhance bioavailability for topical use. *J Drug Deliv Sci Technol.* 2021;61. PMID 102155.
53. Valeeva FG, Vasilieva EA, Gaynanova GA, Kashapov RR, Zakharov SV, Kuryashov DA, *et al.* Supramolecular systems based on hydrotropes, their analogues and mixtures with typical surfactants. Structural behavior, enhanced solubilization and viscosity properties. *JMol Liq.* 2015;203:104-10. doi: 10.1016/j.molliq.2014.12.027.

## PICTORIAL ABSTRACT



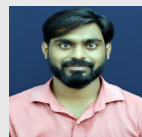
## SUMMARY

The chronological assessment of the solubility enhancement studies of poorly water-soluble Meloxicam has been submitted using sodium benzoate hydrotropic agents. Through this research, we have enclosed the applicability of the hydrotropic solubilization approach in making solid dispersion. Due to Meloxicam's improved solubility and dissolution rate, quick action onset and better absorption are expected. Hydrotropic solid dispersion loaded topical gel is advantageous for enhanced transdermal delivery of poorly soluble drugs. This technique has been suggested to be applied for other poorly soluble drugs.

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