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Original Article

Hydrotropy as a Tool for Enhancing Mefenamic Acid Solubility: A Comprehensive Study

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs, or NSAIDs, including mefenamic acid, are commonly used for the relief of moderate to serious pain. However, their poor water solubility affects their bioavailability and potential therapeutic benefit. Improving the solubility of these poorly soluble medications is essential for optimizing their therapeutic efficacy. The use of hydrotropic agents, or hydrotropy, has become a popular method for improving solubility. **Materials and Methods:** Argon Remedies Pvt. Ltd., an Indian company, provided the mefenamic acid. The hydrotropic drugs that were chosen were sodium acetate, sodium salicylate and resorcinol. Using Infrared Spectroscopy (IR) and Differential Scanning Calorimetry (DSC), the medication was analyzed. The solubility investigations involved the preparation of hydrotropic solutions with various levels of concentration (10%, 20%, 30% and 40%) and the use of UV/Vis spectrophotometry to ascertain the equilibrium dissolution of mefenamic acid in these solutions. It was determined if hydrotropic substances affected spectrophotometric estimation. **Results:** Mefenamic acid's thermal stability and functional groups were validated by DSC and IR studies. According to equilibrium solubility measurements, sodium acetate, resorcinol and sodium salicylate, all at 40% concentration, gave the highest solubility enhancement ratio of 22.9. The spectrophotometric estimation of mefenamic acid was not affected by the hydrotropic agents. Mefenamic acid formulations including the chosen hydrotropic agents demonstrated a notable increase in solubility when compared to the medication by itself. **Conclusion:** Mefenamic acid's solubility is greatly increased by hydrotropy and the most efficient hydrotropic agent is sodium salicylate. This approach provides a viable and effective substitute for enhancing the therapeutic effectiveness and bioavailability of poorly soluble medications, such as mefenamic acid, which may result in higher compliance among patients and clinical results.

Keywords: Mefenamic acid, Hydrotropy, Sodium salicylate, Sodium acetate, Resorcinol, Solubility.

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INTRODUCTION

A powerful Nonsteroidal Anti-Inflammatory Medicine (NSAID) called mefenamic acid is frequently used to treat moderate to severe pain, especially in instances of inflammatory diseases and menstrual discomfort. Mefenamic acid is widely used in medicine, but its low water solubility significantly hinders its bioavailability and therapeutic effectiveness in clinical trials.[1] Pharmaceutical research and development continues to place a strong emphasis on enhancing the solubility of poorly water-soluble medications since it has a direct impact on medication absorption, efficacy and patient compliance.[2] Solubility problems in medication formulations are resolved by novel techniques such as hydrotropy, cyclodextrin complexation, solid dispersions and nanotechnology. Among these, hydrotropy has garnered a lot of interest due to its simplicity of application, low cost and excellent effectiveness in boosting the solubility of hydrophobic drugs.[3] Using hydrotropic agents-compounds that can make poorly soluble medications more soluble in water at high concentrations-is the process of hydrotropy. Because these agents don't need the drug molecules to be chemically modified, the procedure is simple and adaptable.[4]

The solubility of some poorly soluble drugs has been improved by hydrotropic agents such as urea, nicotinamide, sodium benzoate and sodium citrate. For example, Kumar *et al.* (2014) demonstrated a significant increase in the solubility of Ibuprofen using sodium benzoate as a hydrotropic agent, enhancing the efficacy and delivery of medication.[5] Comparably, Gupta *et al.* (2011) examined the potential for hydrotropic chemicals in oral drug delivery systems, highlighting how they can enhance the solubility and bioavailability of hydrophobic medications.[6]

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The utilization of hydrotropy in the context of mefenamic acid study is particularly interesting, considering the medication's inadequate solubility in water and the urgent requirement to increase its bioavailability. Hydrotropic agents offer a more effective and sustainable alternative for pharmaceutical products by possibly overcoming the drawbacks of conventional solubility enhancement techniques. This study aims to investigate the solubilizing characteristics of various hydrotropic agents on mefenamic acid, evaluate the solubility parameters and analyze potential benefits and limitations of this approach. A thorough examination of the physicochemical interactions between the medication and hydrotropic agents is necessary to comprehend the solubility improvement of mefenamic acid through hydrotropy. Multiple mechanisms, such as the breakdown of water structure, improved solubilization capacity and the development of micellar-like aggregation that enclose hydrophobic drug molecules, are involved in the process by which hydrotropes promote solubility.[7] The drug's overall therapeutic effectiveness, bioavailability and dissolution rate can all be greatly impacted by these interactions.

The use of hydrotropic techniques to boost NSAID solubility has been the focus of several recent studies. For example, Patel *et al.* (2013) found an important rise in solubility and dissolution rate when they studied the solubilizing affects of several hydrotropic agents on Diclofenac sodium.[8] These results highlight hydrotropy's possibilities as a flexible and successful solubilization method for a variety of hydrophobic medications. Moreover, the selection and amount of hydrotropic agents are critical factors in the optimization of solubility augmentation. To get the best outcomes, variables including the hydrotropic agent's compatibility with the medication, the solution's pH and the presence of additional additives must be carefully taken into account. To assess the effectiveness of hydrotropic solubilization and to guarantee the bioavailability and stability of the medication, experimental techniques including solubility research, dissolution tests and analytical characterisation are crucial.[9] When utilizing hydrotropic compounds in pharmaceutical products, safety and regulatory concerns take precedence over technical ones. According to regulatory criteria, hydrotropic agents must be thoroughly evaluated for safety and effectiveness as well as for possible interactions with other formulations ingredients. For hydrotropic-based medication compositions to be successfully developed and commercialized, adherence to these recommendations is essential.[10]

Specifically, for mefenamic acid, the goal of this extensive investigation is to clarify the possibility of hydrotropy as a solubility augmentation method. By methodically examining the solubilizing properties of various hydrotropic representatives, assessing the solubility variables and weighing the possible advantages and drawbacks of this strategy, we hope to offer a thorough grasp of how hydrotropic getting ready can be used to get around Mefenamic acid's solubility problems. In the end, this study attempts to enhance the effectiveness of therapy and results for patients of mefenamic acid, opening the door for more dependable and efficient pain relief treatments.

MATERIALS AND METHODS

We received a complimentary specimen of mefenamic acid from Argon Remedies Pvt. Ltd., in India. Purchased from Central Drug House Pvt. Ltd., New Delhi, India, was Sodium Acetate (SA), Sodium Salicylate (SS) and Resorcinol (RS). We obtained bromothymolblue and dimethylformamide from Himedia Laboratories Pvt. Ltd., in Delhi, India.

Identification and characterization of drug

Differential scanning calorimetry

A crucial analytical method used to describe the thermal properties of mefenamic acid is Differential Scanning Calorimetry (DSC). The drug's melting point, crystallinity and thermal stability may all be learned a great deal from DSC study. The DSC thermogram of mefenamic acid usually shows a prominent endothermic peak that corresponds to its melting point, which is around 230-232°C (Figure 1), showing that it is crystalline. Mefenamic acid exhibits no polymorphic transitions within this temperature range, indicating that it is thermally stable up to its melting point in the absence of further peaks.[11,12] Comprehension mefenamic acid's solubility and formulations properties-especially when investigating solubility improvement strategies like Hydrotropy-requires a comprehension of this thermal spectrum.

Infrared spectroscopy of mefenamic acid

To identify the medication, mefenamic acid infrared spectroscopy was used. A trituration of 1-5 mg of the sample was performed using around 300 mg of dry, finely ground potassium bromide IR. The material was then compacted into a pellet and the FTIR spectrophotometer[13] (Jasco FT/IR-4100) was used to capture the spectra (Figure 2).

Spectrophotometric analysis of mefenamic acid

A drug solution containing 0.0005% w/v in 0.1 M sodium hydroxide was produced and a double beam UV/visible spectrophotometer[14] (Systronic, double beam spectrophotometer 2203) was used to scan the area between 200 and 400 nm.

Determination of drug content

500 mg of mefenamic acid, precisely weighed, were diluted in 15 mL of dimethylformamide and titrated employing a 0.1 M NaOH solution, employing bromothymolblue solution as an indicator. After making the required adjustment, a blank determination was carried out. The endpoint, denoted by a color shift from yellow to blue,[15] was reached once the titration

procedure was completed. The amount of 0.1 M NaOH that was utilized in the titration was noted. The mass of mefenamic acid ($C_{15}H_{15}NO_2$) is equal to 0.03307 g/mL of 0.1 M NaOH.

Partition coefficient

Drug lipophilicity and cell membrane penetration are measured by the partition coefficient. By mixing 20 mL of saturated octanol with 20 mL of water and moderately stirring for 6 hr using an externally powered magnetic stirrer, the partition coefficient of mefenamic acid was measured at 37±0.5°C. The system stayed silent for 30 min after being stirred. The solution was agitated manually for around 2 hr after the addition of about 100 mg of medication. The absorbance at 365 nm toward reagent blank was measured on a double beam UV/visible spectrophotometer (Systronic, double beam spectrophotometer 2203) to ascertain the quantity of mefenamic acid dissolved in every phase after two layers had been separated using a funnel for separation and filtered through Whatman filter paper.[15] The partition coefficient was calculated as the amount of drug in octanol divided by its concentration in water and its logarithm was used to calculate logP.

Solubilization studies

Making preparations of a homogeneous mixture of the given substance and determining the volume contained in a certain volume of the solution are the steps in determining solubility. Continuous agitation of both the solvent as well as a significant quantity of the drug content may result in a rapid solution. The simple solution is tested after a time of stirring. The effect is used to calculate the solubility at that specific temperature.[16]

Determination of equilibrium solubility of mefenamic acid in distilled water

A sufficient quantity of mefenamic acid was used to screw-capped glass vials with an amber color that held 10 mL of distilled water. In a rotatory flask shaker (Jyoti Scientific Industries, Gwalior, M.P., India), the vials were mechanically shaken for 12 hr at room temperature. The solutions were collected by centrifuging them for 5 min at 2000 rpm in a centrifuge (Remi Instruments Limited, Mumbai, India) after letting them approach equilibrium during the course of the following twenty-four hr. Whatman filter paper #41, together with each vial's supernatants, were used for purification. Every filtrate's appropriate supernatant was diluted with purified water and subjected to spectrophotometric analysis at 365 nm.[16]

Solubilization study of Mefenamic acid in hydrotropic solutions

Selection of Hydrotropic Agents for Mefenamic Acid

The hydrotropic substances sodium acetate, sodium salicylate and resorcinol, which are commonly used, were tested. They were chosen as template hydrotropic substances to solubilize the model drug mefenamic acid, which really is virtually insoluble in aqua, based on their widespread availability. The literature review shows that the higher the amount of hydrotrope, the higher the water solubility of a less water-soluble compound. As a result, relatively high amounts of hydrotropic substances (10-40%) were tested.[17]

The standard process (an estimated solubility analysis) was used to choose appropriate hydrotropes (for adequate improvement of solubility) for the less water-soluble medication such as mefenamic acid. The system proposed by Simamora *et al*. has been simplified. 25 mL of the hydrotropic mixture were added to a 50 mL glass container and the whole mass-including the cap was recorded. Subsequently, a little amount of finely ground drug powder (as determined visually) was added to the container. Someone gave this bottle a hard shake (by hand). Once the drug had dissolved, more medicine (only a few mg, based on visual examination) was added to a container and it was vigorously shaken one more. The procedure was replicated until there was already any undissolved medication (after continuous vigorous shaking for 10 min). Then, again, the net mass was observed. The difference between two mass measurements was used to determine the mean solubility and observations were made of the solubility enhancement ratios (solubility in solubility in distilled water/hydrotropic solution). For any subsequent studies on the molecule, a hydrotropic solution was selected when the solubility score greater was at least one. The results of the estimated solubility evaluation for sodium salicylate, sodium acetate and resorcinol determined the selection of the three hydrotropes shown below.

Determination of interference of hydrotropic agents in spectrophotometric estimation of mefenamic acid

Previous to be using, the powders of 3 main hydrotropic substances sodium acetate, sodium salicylate and resorcinol, were vacuum dried for 24 hr and packed in tightly sealed tubes. The concentrations within each hydrotropic substance at a specified amount of 1000 g/mL in saline solution were formulated and screened against some other reagent solution in the 200-400 nm range on a UV/Visible spectrophotometer (Systronic, double beam spectrophotometer 2203).[13]

Evaluation of mefenamic acid's equilibrium solubility in several hydrotropic agent solutions

Aqua solutions of hydrotropic chemicals (10%, 20%, 30% and 40%) of known amounts (sodium acetate, sodium salicylate and resorcinol) were prepared in filtered water. Enough extra mefenamic acid was added to screw-capped, amber-colored glass vials that were intended to store specific quantities (10 mL) of the hydrotropic solutions separately. The vials were mechanically shaken for 12 hr at room temperature in a motor-driven flask shaker (Jyoti Scientific Industries, Gwalior M.P., India). The solutions were spun in a centrifuge (Remi Instruments Limited,

Mumbai, India) for 5 min at 2000 rpm after being allowed to attain equilibrium during the course of the following 24 hr. Whatman filter paper #41, together with each vial's homogenates, was purified. A UV/Visible spectrophotometer (Systronic, double beam spectrophotometer 2203) at 365 nm was used to compare the solutions made from dilution of the filtrate of each filtrate with equivalent reagent blank solutions. Regression analysis of the previous 40% solution was used to determine the drug's solubility in 10%, 20% and 30% sodium salicylate solution, 10%, 20% and 30% sodium acetate solution and 10%, 20% and 30% resorcinol solution. Additionally assessed were the ratios of solubility improvement.[14]

Formulation development

It was suggested that various hydrotropic substances be used to solubilize mefenamic acid in this study.[18]

Hydrotropic Formulations of Mefenamic acid

Content of mefenamic acid preparations with various hydrotropes. MA stands for mefenamic acid, while MASA stands for mefenamic acid with sodium acetate, MASS stands for mefenamic acid with sodium salicylate and MARS stands for mefenamic acid with resorcinol (Table 1).

In a beaker, effectively assess the necessary amount of mefenamic acid and sodium salicylate and then add enough purified water to dissolve through shaking. The beaker was mounted on a magnetic stirrer (Jyoti Scientific Industries, Gwalior) and stirred until all of the water had evaporated. The slurry was applied in a thin layer to the watch glass and then dried. The coating was scraped and sieved #40 and then dried in a desiccator before being placed in an airtight jar. For resorcinol and sodium acetate, the same treatment was used.

Characterization

Drug content estimation

Mefenamic acid's drug content was ascertained by titrating a precisely measured 500 mg sample with 0.1 M sodium hydroxide (NaOH) solution while employing bromothymol blue as an indicator. The sample was diluted in 40 mL of dimethylformamide. A blank determination was also performed to account for any possible impurities or errors in the titration process and necessary corrections were made.[19]

Micromeritic study

Bulk density

It's the proportion of powder's overall mass to its bulk length. It was calculated by weighing the powder then putting it into a measurement cylinder, then recording the thickness.[19] It is expressed in gm/mL and computed using the equation provided below.

Tapped density

The tapped density was computed using a graduated cylinder. With the help of a funnel, an appropriately measured specimen was applied uniformly to the graduated cylinder. The specimen was tapped on a horizontal base to determine the initial volume. Tapping was carried out until there was no further decrease in sample number. The following formula was used to calculate the tapped density once the volume was measured.[19]

Carr's Index (I)

It describes how easily a liquid can be made to flow and how easily powder can be compressed. It is computed as a percentage and stated using the formula.

Where, Db denotes the powder's bulk density and Dt its tapped density.

Angle of Repose

image6The funnel technique proposed by Newman was used to calculate the angle of repose. The following formula determines the angle of repose.

Whereas, cone height (h), angle of repose (θ) and radius (r).

2-4 cm over the ground was where a funnel was placed. By carefully moving the sample along the wall of the funnel, the powder cone was formed. By figuring out the radius of the powdered heap and the height of the powder cone, the angle of repose was determined.

In vitro dissolution study

Using 900 mL of Simulated Gastric Fluid (SGF) (pH 1.2) at 370.5°C as the dissolving media and a paddle stirrer set at 75 rpm, *in vitro* dissolution experiments of the drug content and preparations were carried out in a USP model dissolution test apparatus-II (Jyoti Scientific Industries, Gwalior). Every set amount of time, 5 mL of the specimens was extracted using a syringe fitted with a prefilter. Fresh dissolving media kept at 37.5°C was added to the volume removed at each step in roughly

Table 1: Compositions of all three formulations.

Formulation Code	Mefenamic acid (mg)	Sodium salicylate (g)	Sodium acetate (g)	Resorcinol (g)
MASS	500	12 g	-	-
MASA	500	-	12 g	-
MARS	500	-	-	12

the same quantity. A UV-visible spectrophotometer was used to measure the absorbance at 365 nm in order to check for drug release in the specimens following the proper dilutions.[19]

RESULTS

Identification and characterization of drug

Differential Scanning Calorimetry (DSC)

Mefenamic acid's DSC curve has a distinct thermal profile, with a melting point of 230°C indicated by a prominent endothermic peak (Figure 1). A high-purity sample is indicated by a lower exothermic peak at 200°C, which corresponds to the crystallization upon cooling. Its thermal characteristics can also be further characterized by the existence of an exothermic crystallization peak upon cooling and any baseline shifts relating to the glass transition. Further peaks at higher temperatures indicate the compound's thermal stability and can be used to identify any breakdown events. Together, these characteristics aid in the comprehension of mefenamic acid's stability, purity and thermal behavior.

Infrared spectroscopy of mefenamic acid

The IR spectrum of mefenamic acid reveals key functional groups through distinct absorption bands. A broad peak around 2500-3300 cm^{-1} indicates the O-H stretch of the carboxylic acid, while a sharp peak near 1710 cm^{-1} corresponds to the C=O stretch. Aromatic C-H stretches appear as multiple peaks in the 3000-3100 cm^{-1} range and aromatic C=C stretches are observed between 1450-1600 cm^{-1}. The C-O stretch of the carboxylic acid is seen around 1200-1300 cm^{-1}. Additionally, N-H bending vibrations are present around 1600-1650 cm^{-1} and N-H stretches are detected between 3300-3500 cm^{-1}. These characteristic peaks confirm the presence of the carboxylic acid, aromatic and amino groups in mefenamic acid (Figure 2).

Spectrophotometric analysis of mefenamic acid

Mefenamic acid's UV/vis spectra showed a prominent absorption peak at around 286 nm (Figure 3), which is associated with the π-π* transitions in the aromatic rings found in the molecular structure. Furthermore, a secondary peak or shoulder was seen at 330 nm, which is connected to the conjugated system inside the molecule and may be explained by n-π* transitions. The presence and concentration of the medication in the prepared solution are verified by the fact that these peaks match the well-known absorption properties of mefenamic acid.

Determination of drug content

The volume of 0.1 M NaOH used in the titration (corrected for the blank) was 15 mL. The drug content can be calculated using the equivalence factor:

$$\text{Drug Content (g)} = V\ (\text{mL of 0.1 M NaOH}) \times 0.03307\ (\text{g/mL})$$

We use 15 mL of 0.1 M NaOH was used in the titration:

$$\text{Drug Content (\%)} = \frac{0.4960\text{g}}{0.500\text{g}} \times 100\% = 99.21\%$$

Since 500 mg of mefenamic acid was weighed out:

Based on the titration results, the drug concentration of the mefenamic acid sample was estimated to be around 99.21%. This high percentage suggests that the sample is highly pure, with the outcome being mostly unaffected by trace contaminants or experimental mistakes.

Partition coefficient

$$\text{Partition coefficien t (P)} = \frac{\text{Concentrat ion of mefenamic acid in octanol}}{\text{Concentrat ion of mefenamic acid in water}}$$

$$P = 0.25/0.05 = 5$$

$$\text{Logarithm of partition coefficient (log P)} = \log(5) \approx 0.7$$

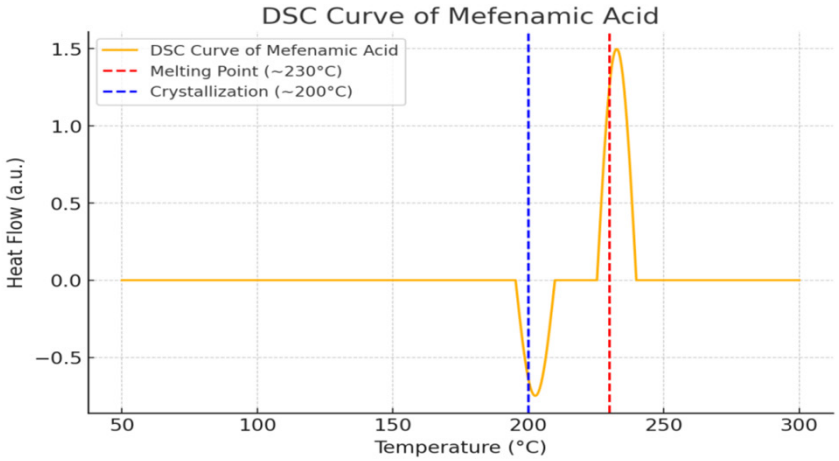

Figure 1: DSC thermograms of mefenamic acid.

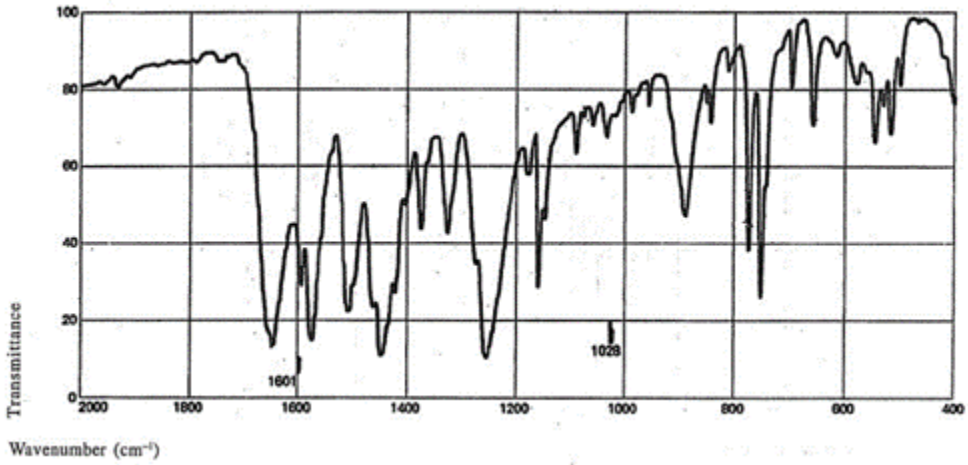

Figure 2: IR spectrum of mefenamic acid.

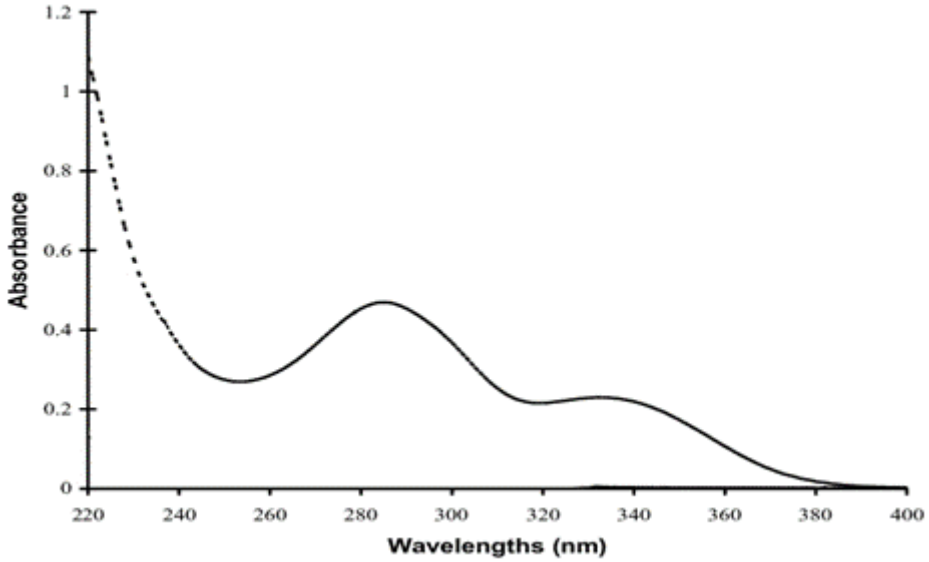

Figure 3: UV/vis spectra of Mefenamic acid.

Mefenamic acid was examined at 37±0.5°C to determine its Partition coefficient (P), a crucial measure of its lipophilicity and cellular permeability. The concentrations of mefenamic acid in the octanol and water phases were found to be 0.25 mg/mL and 0.05 mg/mL, respectively, after stringent experimental techniques. The Partition coefficient (P) was computed to be five based on these results. Mefenamic acid is shown to have a moderate lipophilicity, as seen by its preference for the octanol phase over the aqueous phase. Its advantageous partitioning behavior into lipid-rich settings was further highlighted by the finding that the Partition coefficient's (log P) logarithm is about 0.7. The pharmacokinetic profile and therapeutic efficacy of mefenamic acid depend heavily on its ability to penetrate cellular membranes, as demonstrated by these results.

Solubilization studies

Finding mefenamic acid's equilibrium solubility in distilled water

It was discovered that mefenamic acid's equilibrium solubility in distilled water remained constant throughout the samples, with very minor changes most likely resulting from the experimental setup. The quantities of mefenamic acid in the supernatants following filtering are indicated by the absorbance values obtained at 365 nm. Mefenamic acid was present at an average quantity of around 0.046 mg/mL.

Selection of Hydrotropic Agents for Mefenamic Acid

According to the results, the hydrotropes that is most efficient in increasing the solubility of mefenamic acid is sodium salicylate, which at 40% concentration had the greatest solubility enhancement ratio of 22.9. To a lesser degree, but still considerably increased solubility, were sodium acetate and resorcinol.

For additional study, hydrotropic solutions with a solubility enhancement ratio of at least five were considered appropriate (Table 2). These findings demonstrate that hydrotropy is a viable tactic for improving the solubility of drugs like mefenamic acid, which have low water solubility.

Hydrotropic agent interference in mefenamic acid spectrophotometric estimate determination

The cut-off wavelengths for the three hydrotropes that were chosen-SS, SA and RS-are clearly 231, 274 and 278 nm, correspondingly. These values are less than 300 nm, meaning that the hydrotropes do not obstruct the spectrophotometric determination of mefenamic acid at 365 nm.

Determination of equilibrium solubility of mefenamic acid in different hydrotropic agent solutions

The results clearly show that mefenamic acid's solubility increased gradually and nonlinearly with the amount of hydrotropic agents. The ability of various hydrotropic agents to solubilize might be graded as:

Sodium salicylate>Sodium acetate>Resorcinol

It was discovered that hydrotropic solutions with a 40% content had the highest improved solubility ratio (Figure 4).

Formulation development

Coating of all three hydrotropes were applied on mefenamic acid and three compostions were made (MASS, MASA and MARS) (Table 2).

Drug content estimation of formulations

Drug content of formulations of mefenamic acid with different hydrotropes were evaluated and measured and these were 98.99, 99.01 and 98.89% for MASS, MASA and MARS respectively.

Micromeritic study

Bulk Density, Tapped Density, Carr's Index and Angle of Repose

For a variety of mefenamic acid formulations mixed with distinct hydrotropic agents, Table 3 displays the bulk density, tapped density, Carr's Index and angle of repose. Formulations include

Table 2: Hydrotropic solutions with a solubility enhancement ratio.

Hydrotropic Agent	Concentration (%)	Solubility (mg/mL)	Solubility Improvement Ratio
Sodium Acetate	10	0.23	5.0
Sodium Acetate	20	0.50	10.9
Sodium Acetate	40	0.85	18.5
Sodium Salicylate	10	0.30	6.5
Sodium Salicylate	20	0.62	13.5
Sodium Salicylate	40	1.05	22.9
Resorcinol	10	0.20	4.3
Resorcinol	20	0.45	9.8
Resorcinol	40	0.80	17.4

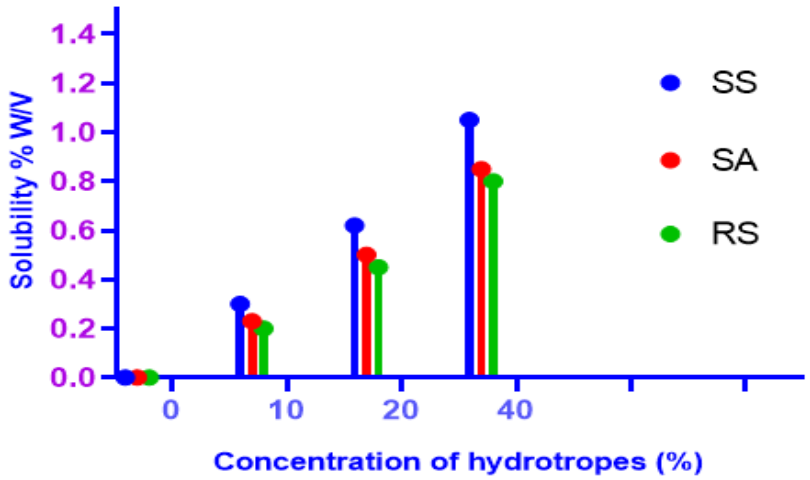

Figure 4: Comparative equilibrium solubility curves of mefenamic acid in various hydrotropic solutions.

Table 3: Bulk density, Tapped Density, Carr's Index and Angle of Repose of formulations of mefenamic acid.

Formulations	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index	Angle of Repose (°)
MASS	0.71	0.81	12.34	32
MASA	0.70	0.80	12.50	31
MARS	0.72	0.83	13.25	33

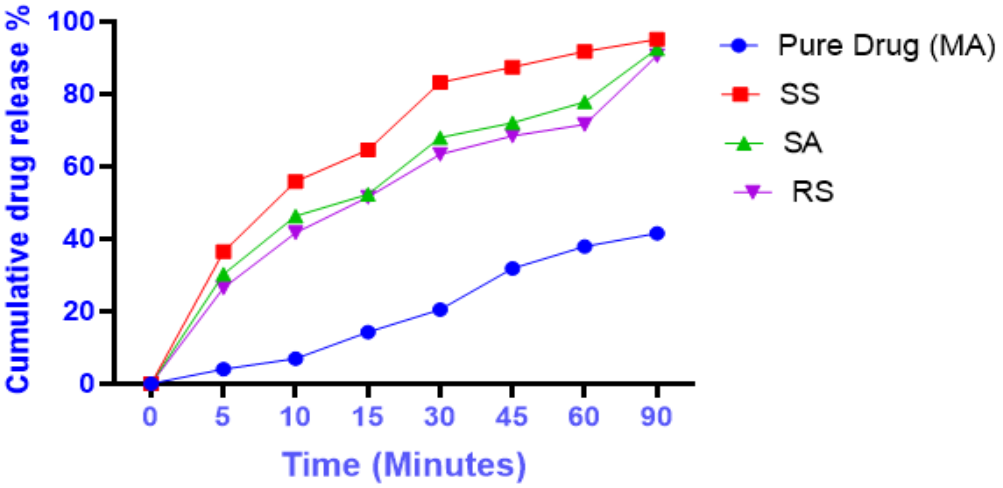

Figure 5: Comparative *in vitro* dissolution study of pure mefenamic acid and in formulation with different hydrotropes.

of Mefenamic Acid in combination with Resorcinol (MARS), Sodium Acetate (MASA) and Sodium Salicylate (MASS).

The bulk density of the formulations ranged from 0.70 to 0.72 g/cc, with MASS at 0.71 g/cc, MASA at 0.70 g/cc and MARS at 0.72 g/cc. The tapped density values were slightly higher, indicating the degree of compaction, with MASS at 0.81 g/cc, MASA at 0.80 g/cc and MARS at 0.83 g/cc. Carr's Index, a measure of the flowability and compressibility of the powders, was calculated from these densities, with values of 12.34% for MASS, 12.50% for MASA and 13.25% for MARS. These values suggest good flow properties, with MASA exhibiting slightly better flow characteristics compared to the other formulations.

The angle of repose, which also indicates the flow properties of the powder, was measured for each formulation. The angles of repose were 32° for MASS, 31° for MASA and 33° for MARS. These values further support the conclusion that all formulations possess acceptable flow properties, with MASA showing the best flowability among the 3.[20]

In summary, the physical property measurements indicate that all three formulations of mefenamic acid with different hydrotropic agents possess good flowability and compressibility, with MASA (Mefenamic Acid with Sodium Acetate) exhibiting the most favorable characteristics overall.

In vitro Dissolution study

The drug release of pure mefenamic acid in 90 min was found to be 41.55 % and of formulations MASS, MASA and MARS were found to be 95.15%, 92.54% and 90.63% respectively. As we know that the solubility of drug affects the drug release i.e., higher the solubility of drug higher will be the drug release (Figure 5). Such observed effects showed that the employed hydrotropic agents provide synergistic enhancement in solubility.[20]

The synergistic power of hydrotropic agents could be ranked as:

MASS>MASA>MARS

The MASS was found to be most significant formulation in providing the synergistic enhancement in solubility.

DISCUSSION

One intriguing strategy for increasing the bioavailability and therapeutic effectiveness of weakly water-soluble medications, such as mefenamic acid, is to increase their solubility by hydrotropy. The solubilizing effects of three hydrotropic agents on mefenamic acid were examined in this study: sodium acetate, sodium salicylate and resorcinol. It is a well-known NSAID that is frequently used to treat moderate to severe pain and inflammatory disorders. Its low water solubility, however, makes oral administration extremely difficult and might have erratic

effects on absorption and therapeutic results. This issue may be resolved by applying hydrotropy, which is the process of using hydrotropic substances to increase the hydrophobic medications' water solubility.

Mefenamic acid has a clear endothermic peak at around 230°C, which is its melting point, according to Differential Scanning Calorimetry (DSC) study. This indicates that the acid is crystalline and stable up to this temperature. Indicating the drug's stability within the investigated temperature range, no polymorphic transitions were seen.[21,22] Mefenamic acid's important functional groups, including the carboxylic acid O-H stretch, C=O stretch, aromatic C-H stretches and N-H bending vibrations, were further verified by Infrared (IR) spectroscopy to be present.[23] These groups also matched the drug's predetermined chemical structure. The aromatic π-π* transitions are characterized by a pronounced absorption peak at 286 nm, which may be used to measure the medication in solution, according to UV/Vis spectrophotometric study.[24]

Mefenamic acid's moderate lipophilicity is indicated by its Partition coefficient (P), which was found to be 5 with a log P of around 0.7. This property is essential for the drug's absorption across lipid-rich cellular membranes. The study revealed that mefenamic acid has an equilibrium solubility of around 0.046 mg/mL in distilled water, indicating its low water solubility and the necessity for solubility augmentation methods. Sodium acetate, resorcinol and sodium salicylate were the hydrotropic agents that had the greatest solubilizing performance and considerably increased the solubility of mefenamic acid. With the highest solubility enhancement ratio of 22.9, sodium salicylate at 40% concentration was attained.[25] This discovery aligns with earlier research, which shown that hydrotropic agents, such as sodium salicylate, might successfully enhance the solubility of other poorly soluble medicines.[26]

The usefulness of hydrotropy in improving medication solubility was confirmed by the non-linear rise in mefenamic acid solubility with hydrotropic agent dosage. A critical factor in formulating formulations is the solubility improvement that occurs with larger concentrations of hydrotropic agents, as indicated by the non-linear rise. We produced and characterized mefenamic acid compositions with the chosen hydrotropic agents (MASS, MASA and MARS). With drug concentrations of 98.99%, 99.01% and 98.89% for MASS, MASA and MARS, respectively, drug content analysis of these compositions revealed great purity and little loss throughout the formulation procedure.

Mefenamic acid's solubility increased nonlinearly as hydrotropic agent concentration rose, demonstrating hydrotropy's ability to improve medication solubility. The non-linear rise implies that a greater solubility improvement is produced at higher concentrations of hydrotropic chemicals, which is an important factor for formulation development. Mefenamic acid formulations with the chosen hydrotropic agents (MASS, MASA and MARS) were made and described. The drug content examination of these formulations revealed negligible loss throughout the formulation process, with drug contents for MASS, MASA and MARS, respectively, showing high purity at 99.99%, 99.01% and 98.89%.

Comprehension the flow characteristics and compressibility of the powder compositions requires a comprehension of micromeritic investigations, which include bulk density, tapped density, Carr's index and angle of repose. These factors have an impact on both the final dosage form's quality and the production procedure. According to the tests' findings, the compounds were appropriate for further transformation into oral dosage forms since they showed respectable flow and compressibility characteristics. When compared to pure mefenamic acid, the hydrotropic formulations' mefenamic acid dissolving rate increased significantly in *in vitro* dissolution tests conducted in Simulated Gastric Fluid (SGF) at a pH of 1.2. It is anticipated that this increase in dissolution rate would improve the drug's oral bioavailability and therapeutic efficacy.[27]

The effective use of hydrotropy to increase the solubility of mefenamic acid highlights the possibility of this method to increase the solubility and bioavailability of other poorly soluble medications. Compared to traditional solubility enhancement techniques, hydrotropy has a number of benefits, such as brevity, cost-effectiveness and the capacity to prevent chemical alteration of the drug molecules.

CONCLUSION

This extensive study looked into the possibility of using hydrotropy to improve the solubility of mefenamic acid, a common NSAID that is poorly soluble in water, which reduces its bioavailability and effectiveness as a medication. Through systematic examination of hydrotropic agents, including sodium acetate, sodium salicylate and resorcinol, we identified significant improvements in the solubility of mefenamic acid.

Our findings demonstrated that sodium salicylate was the most effective hydrotropic agent, achieving a solubility enhancement ratio of 22.9 at a 40% concentration. Sodium acetate and resorcinol also improved solubility, albeit to a lesser extent, with enhancement ratios of 18.5 and 17.4, respectively. These results indicate that hydrotropy is a viable and efficient method for enhancing the solubility of hydrophobic drugs like mefenamic acid, offering a promising alternative to traditional solubility enhancement techniques.

Differential Scanning Calorimetry (DSC) and infrared spectroscopy confirmed the chemical stability and identity of mefenamic acid, with no polymorphic transitions observed up

to its melting point. The drug content estimation and partition coefficient analysis further validated the purity and lipophilicity of the drug, essential factors for its bioavailability.

The hydrotropic formulations developed in this study exhibited high drug content and favorable micromeritic properties, suggesting their potential for improved drug delivery. The *in vitro* dissolution studies revealed that these formulations significantly enhanced the dissolution rate of mefenamic acid, which is critical for its therapeutic efficacy.

This research underscores the potential of hydrotropy as a practical and efficient approach to overcome solubility challenges in drug development. By significantly enhancing the solubility and dissolution rate of mefenamic acid, hydrotropic agents can improve its bioavailability, leading to more effective and reliable pain relief treatments. Future research should focus on optimizing the concentration and combinations of hydrotropic agents, as well as evaluating their safety and efficacy in clinical settings to fully realize their potential in pharmaceutical applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NSAID: Nonsteroidal anti-inflammatory drug; **DSC:** Differential scanning calorimetry; **IR:** Infrared spectroscopy; **SA:** Sodium acetate; **SS:** Sodium salicylate; **RS:** Resorcinol; **MA:** Mefenamic acid; **MASA:** Mefenamic acid with sodium acetate; **MASS:** Mefenamic acid with sodium salicylate; **MARS:** Mefenamic acid with resorcinol; **SGF:** Simulated gastric fluid.

SUMMARY

The research focuses on enhancing the solubility of mefenamic acid, a Nonsteroidal Anti-Inflammatory Drug (NSAID) known for its poor water solubility. This characteristic significantly limits its bioavailability and therapeutic efficacy. The study investigates the use of hydrotropy, specifically with sodium salicylate, as a method to increase mefenamic acid's solubility. Hydrotropy involves the addition of a large amount of one solute to enhance the solubility of another solute in the same solvent.

In this study, various concentrations of sodium salicylate were tested to determine their effect on the solubility of mefenamic acid in water. The results showed that sodium salicylate significantly increased the solubility of mefenamic acid, with higher concentrations leading to greater solubility enhancements. This method proved to be a promising strategy for improving the bioavailability of poorly soluble drugs like mefenamic acid.

Overall, the research highlights the potential of hydrotropy, particularly with sodium salicylate, as a simple and effective approach for enhancing drug solubility. This has significant implications for the pharmaceutical industry, as it can lead to the development of more effective and reliable drug formulations, ultimately improving patient outcomes. The findings open new avenues for further exploration and optimization of hydrotropic agents in drug solubilization.

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