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Investigation of the Solubility Enhancement of Aceclofenac by Mixed Hydrotropes at Minimal Safe Concentrations

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article.

Abstract

Background: Aceclofenac is categorized as a Class II drug under the Biopharmaceutics Classification System, which inherently exhibits low solubility and bioavailability. The drug's poor aqueous solubility significantly impedes its absorption. Hence, significant research efforts are directed toward various strategies to improve its aqueous solubility and dissolution. Various sophisticated formulation strategies have been developed to overcome this limitation. Among them is the hydrotropic solubilization technique, which offers a simple, promising and more biocompatible alternative that does not require chemical modification of hydrophobic drugs.

Objectives: This study aimed to investigate the solubility-enhancing effect of individual hydrotropes on aceclofenac and to evaluate the solubility-enhancing effect of a mixed hydrotropic system.

Methodology: Solutions of the drug were prepared in methanol to obtain the calibration curve, and the absorbance was read at $\lambda \approx 273.2$. Hydrotropes (urea, sodium benzoate, and sodium citrate) of analytical grade were prepared at concentrations of 1, 2, 4, 6 and 10% w/v, respectively. The solubility enhancement of aceclofenac was determined using UV – Visible spectrophotometry. Blends containing the three hydrotropes were also analysed. Thin Layer Chromatography (TLC) and Fourier Transform Infrared (FTIR) spectroscopy were used to investigate possible complexation of the drugs and hydrotropes.

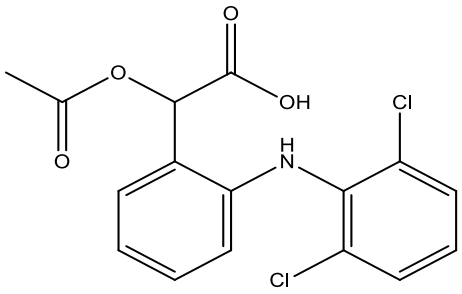
Results: The 10 %w/v sodium citrate hydrotrope gave the highest solubilizing effect (solubility enhancement ratio of 365.80). At 1 %w/v concentration of the mixed hydrotropes (urea, sodium benzoate, sodium citrate), the solubility enhancement ratio was found to be 102.49. The TLC and FT-IR studies showed no interactions between functional groups in the drugs and hydrotropes.

Conclusion: The three hydrotropes investigated enhanced the aqueous solubility of aceclofenac. Mixed hydrotropes (urea, sodium citrate and sodium benzoate) at 1 % w/v gave the highest solubility enhancement ratio; thus suggesting that mixed hydrotropes are a preferred vehicle for the aqueous solubility enhancement of aceclofenac.

Keywords: Aceclofenac, Hydrotropic Solubilization, Mixed Hydrotropic System, Solubility

INTRODUCTION

Aceclofenac (Fig 1), a non-steroidal anti-inflammatory drug, is widely prescribed for conditions such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis due to its efficacy in reducing pain and inflammation (Garg et al., 2021). However, its therapeutic utility is often limited by its poor aqueous solubility, which presents significant challenges for formulation development and subsequent bioavailability (Sarkar et al., 2022). This inherent characteristic, stemming from its high lipophilicity, necessitates innovative approaches to enhance its solubility and improve its pharmacokinetic profile (Patel et al., 2026). Traditional methods to overcome poor drug solubility, such as micronization or salt formation, often have their limitations, including reduced stability or complex manufacturing processes (Sheelarani et al., 2022). Consequently, the pharmaceutical industry continues to explore advanced strategies to address this prevalent issue, particularly for drugs like aceclofenac, where suboptimal solubility can significantly impede therapeutic outcomes (Rahman & Haider, 2023).



2-[(2,6-dichlorophenyl) amino] phenyl acetoxy acetic acid

Figure 1. Chemical structure of aceclofenac

One promising avenue for enhancing the aqueous solubility of class 2 drugs is the use of mixed hydrotropes, which can synergistically increase solubility at concentrations lower than those required by individual hydrotropes, thereby minimizing potential toxicity and improving the safety profile of the final formulation (Sheelarani et al., 2022). This method is particularly attractive given that over 40 % of orally administered immediate-release drug products suffer from poor aqueous solubility, leading to incomplete dissolution and limited oral bioavailability (Vinarov et al., 2018). Indeed, the poor solubility of a drug can significantly impede the development of effective parenteral and oral formulations, necessitating alternative solubilization methods to circumvent the use of potentially harmful organic solvents (Karajgi & Potadar, 2020). In addition, conventional solubilization techniques such as micronization, inclusion complex formation, or cosolvency often face limitations in efficacy or practicality, failing to adequately address the inherent challenges of poorly water-soluble drugs (Kumari et al., 2023). For instance, while lipid-based non-particulate drug delivery systems can enhance the oral absorption of hydrophobic drugs by bypassing the dissolution step, the unpredictable nature of improved oral bioavailability and the potential for drug precipitation upon aqueous dilution remain significant hurdles (Sheelarani et al., 2022). The pharmaceutical industry consistently identifies that approximately 40 % of new chemical entities exhibit poor aqueous solubility, posing significant challenges for drug development and therapeutic effectiveness (Bhalani et al., 2022). This low solubility not only limits their pharmacological potential but also impacts pharmacokinetics, pharmacodynamics, and other important parameters like drug distribution and absorption. Consequently, developing effective solubility enhancement techniques is paramount for a substantial portion of new chemical entities, particularly those categorized as Class II and IV under the Biopharmaceutics Classification System, which inherently exhibit low solubility and bioavailability (Bhalani et al., 2022). The poor aqueous solubility of these drug candidates significantly impedes their progression through drug discovery and clinical trials, highlighting the critical need for advanced solubilization strategies (Kolluru et al., 2021).

Significant research efforts are directed toward various strategies, including complexation, to improve the aqueous solubility and dissolution of such compounds, ultimately enhancing their bioavailability (Munnangi et al., 2023). Consequently, various sophisticated formulation strategies have been developed to overcome this limitation, including the use of nanoparticles, lipid-based drug delivery systems, and amorphous solid dispersions (Patil et al., 2021).

Among these, hydrotropy, a phenomenon where certain substances enhance the solubility of poorly water-soluble compounds in aqueous solutions, offers a promising and often more biocompatible alternative (SAHU, 2021). These hydrotropic agents, typically small amphiphilic molecules, achieve solubilization through molecular interactions that prevent drug aggregation without forming a micellar structure, offering a distinct advantage over traditional surfactant-based methods (Kolluru et al., 2021). Unlike micellar solubilization, which relies on exceeding a critical micelle concentration, hydrotropes enhance solubility through molecular interactions with the solute and water, thereby increasing the apparent solubility of poorly water-soluble drugs without forming organized supramolecular structures (Bolla, 2020). This distinction is crucial, as it allows for the use of lower concentrations of solubilizing agents, thereby mitigating potential toxicological concerns associated with higher surfactant levels (Xie et al., 2024). This approach is particularly beneficial for improving the bioavailability of poorly water-soluble drugs (Kumari et al., 2023).

This present study focused on finding out the most economical, convenient and safe method to enhance the solubility of aceclofenac using hydrotropic agents: urea, sodium benzoate and sodium citrate as well as blends of the hydrotropes at lowest safe concentration for a more effective therapeutic application. To the best of our knowledge, the very low safe concentrations of the hydrotropes used in this study have not been established in any literature. This study also gives good insight into the in vitro-in vivo (IVIV) performance correlations and the extent of solubility enhancement of acecofenac obtainable with blends of the studied hydrotropic agents at minimal safe concentration (Sheelarani et al., 2022).

MATERIALS AND METHODS

Materials

Aceclofenac (Sigma Chemical Company, St. Louis, MO, USA). Sodium benzoate, sodium citrate and urea (Fischer Scientific, USA). Shimadzu UV-1800 UV/Visible Scanning Spectrophotometer; 115 VAC, UV lamp for TLC Visualization (UV lamp 254 nm Sulpeco product India**)**, Vacuum drying oven FO19040.110 Stainless Steel Digital Forced Air Convection Drying Sterilizing Oven, 110V, 50/60 Hz, 1000W, 300 Degree, Constant incubator shaker (Shaker (Labec ZWY-100D Constant Incubator Shaker**)**, FTIR machine Apodization: Happ-Genzel Agilent:4300, Cary 600 series with Resolution Range of 4000 – 650 cm^{-1}.

Methods

Preparation of single and mixed hydrotropes in w/v% concentration for solubility study

Hydrotropes (urea, sodium benzoate, and sodium citrate) at concentrations of 1, 2, 4, 6, and 10% w/v, respectively, were prepared. A 10% w/v solution of each hydrotrope was prepared by weighing 10 g of each hydrotrope in a beaker, dissolving it in a minimal amount of distilled water, transferring the solution to a 100 ml volumetric flask, and diluting to volume with distilled water. Other lower concentrations of the hydrotropes were prepared by dilution with distilled water. The mixed hydrotropes) were similarly prepared (2% urea+ 6% sodium benzoate), (6 %urea + 2% sodium benzoate), and the blend of three hydrotropes (2% urea + 2% sodium benzoate + 2% sodium citrate) was also similarly prepared.

Drug solubility determination

The solubility of aceclofenac was determined using the saturating shake-flask method as described by Alizadeh *et al.* (2018). An excess amount of drug was added to screw-capped 10 ml vials containing 5 ml of purified water, with different concentrations of hydrotropes, respectively. The vials and the mixtures were shaken for 48 h at room temperature (25 ±1 °C) on a rotary flask shaker at a speed of 125 rpm to achieve equilibration. Following equilibration, the samples were filtered through a 0.45 µm disk filter paper, and the supernatants were suitably diluted. The amount of acecofenac was determined by measuring absorbance at $\lambda \approx 273.2$ *nm*. Solubility determination experiments were carried out in triplicate and the results were expressed as mean ± standard deviation. (Karajgi, & Potadar, 2020).

Determination of interference of hydrotropic agents in the estimation of aceclofenac

Thin-layer chromatographic (TLC) studies were performed as described by Kulkarni et al. (2020). A silica gel G 254 plate was activated at 110°C for 1 h. The aqueous solution of drugs alone, hydrotropic solution, as well as solubilized product of

aceclofenac in hydrotrope solution were spotted on the baseline with the aid of a microdropper. The plate was left for 10 minutes to dry and was transferred to a solvent jar saturated with a solvent system mixture of chloroform, methanol and ammonia solution (48:11.5: 0.5 v/v/v). The solvent system was allowed to run for a height of about 5 cm. The plate was transferred to an oven maintained at 80°C for 5 min, then observed under UV light at 253 nm to visualize spots. Retardation factor, Rf was calculated thus:

$$\frac{distance\ travelled\ by\ the\ solute}{distance\ travelled\ by\ the\ solvent}$$ Equation 1.

Fourier transform infrared (FTIR) spectroscopy.

The method of Penjuri et al. (2017) was used to obtain the FTIR spectra for the pure aceclofenac and the prepared blends of hydrotropes containing the aceclofenac. A smear thin film of the samples was placed on a NaCl crystal cell using a capillary tube. The NaCl cells with the samples were placed in the sample holder of the equipment. The samples were scanned from 4500 – 450 cm^{-1} and the spectra generated by the pure drugs, blends of hydrotropes and aceclofenac were matched.

RESULTS

Calibration curve of aceclofenac:

A plot (Fig 2) of the absorbance versus concentration of aceclofenac is a linear curve within the concentration range of 4 – 24 µg/ml. The correlation coefficient of the curve was found to be 0.997. The regression equation defining the linearity of the curve is A = 0.005C + 0.028

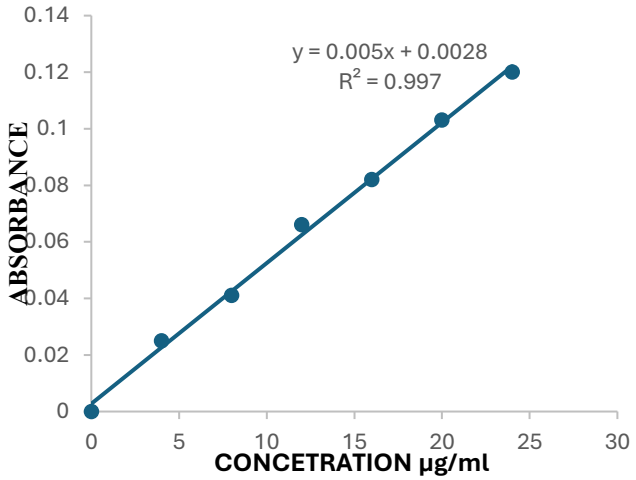


Figure 2: Calibration curve for aceclofenac

The results in Table 1 summarize the solubilizing effects of the hydrotropes studied and the solubility enhancement ratios of the hydrotropes on aceclofenac. Among the three hydrotropes, sodium citrate showed the highest solubilizing effect, followed by sodium benzoate and urea. The solubilizing effect of all the hydrotropes increased with an increase in their concentration as shown in the results below. For the solubility enhancement ratio of the three hydrotropes, sodium citrate showed the highest solubility enhancement ratio of 365.80, followed by sodium benzoate 245.85, and urea 28.81. The solubility enhancement ratio of all the hydrotropes on aceclofenac also increased with an increase in their concentration, as shown in Table 1. Results of solubility determinations are expressed in mean ± standard deviation.

Table 1: Effect of urea, sodium benzoate, and sodium citrate on the aqueous solubility of aceclofenac

Concentration (µg/ml)	**Solubility (µg/ml)**					
	Sodium benzoate **Mean ± SD**	*SER*	**Sodium citrate Mean ± SD**	*SER*	**Urea Mean ± SD**	*SER*
0.0	41.18±0.00	1.00	41.18±0.00	1.00	41.18±0.00	1.00
1	1624.00±0.04	39.44	2124.00±0.61	51.58	386.40±0.04	9.38
2	2584.00 ±0.10	62.75	6024.00±0.32	146.28	622.40±0.07	15.11
4	4364.00±0.03	105.97	10944.00±0.21	265.76	900.40±0.03	21.86
6	6604.00±0.12	160.37	11384.00±0.06	276.44	1138.40±0.27	27.64
10	10124.00±0.32	245.85	15064.00±0.08	365.80	1186.40±0..14	28.81

SER = Solubility enhancement ratio

The results in Table 2 summarize the solubility enhancement effect of the blends of hydrotropes at very minimal concentrations. The blends are sodium benzoate and urea, sodium citrate and urea, and sodium benzoate and sodium citrate. The combined hydrotropes (2% sodium benzoate + 6% sodium citrate) showed the highest increase in solubilization of aceclofenac, with 289.10 folds increase in the solubility of aceclofenac.

Table 2: Effect of mixed hydrotropes on the aqueous solubility of aceclofenac

Concentration of mixed hydrotrope (% w/v)		Solubility (µg/ml)	Enhancement ratio
Sodium benzoate (% w/v)	Urea (% w/v)		
6	1	6884.00±1.06	147.74
1	6	4304.00±1.99	104.52
2	6	7984.00±1.31	193.88
6	2	6084.00±1.12	167.17
Sodium citrate (% w/v)	Urea (% w/v)		
6	1	11564.00±0.73	280.82
1	6	2244.00±1.14	55.95
2	6	11864.00±0.56	288.10
6	2	7304.00±0.85	177.37
Sodium benzoate (% w/v)	Sodium citrate (% w/v)		
6	1	11664.00±1.01	283.24
1	6	9724.00±1.48	236.13
2	6	11864.00±1.00	289.10
6	2	10184.00±1.55	247.30

The results of the Thin Layer Chromatography study of the interactions between aceclofenac and hydrotropes are given in the table below. The results revealed that there is nearly no considerable change in Rf value of aceclofenac solubilized in the solvent system (chloroform, methanol and ammonia solution), and aceclofenac solubilized in the hydrotropic blend solution as all are approximately the same.. Therefore, there is no salt or complex formation of aceclofenac with the hydrotrope molecules as new Rf value was not observed with aceclofenac solubilized in the hydrotropes.

Table 3: Thin-layer chromatography (TLC) Studies to Check aceclofenac – Hydrotrope Interaction

Sample	Distance moved by solvent front)(cm)	Distance moved by drug (cm)	Retardation factor, R_f	R_f·100 (%)
AW	5.00	3.70	0.74	74.00
BA	5.00	3.40	0.68	68.00
UA	5.00	3.60	0.72	72.00
CA	5.00	3.60	0.72	72.00
***B**	5.00	1.70	0.34	34.00
***U**	5.00	1.50	0.30	30.00
***C**	5.00	1.80	0.36	36.00

A= aceclofenac, W= Water (chloroform, methanol and ammonia solution), B= Sodium benzoate, U= Urea and C = Sodium citrate

Fourier Transform Infrared (FTIR) Spectra

The FTIR spectra of a pure sample of aceclofenac and the aceclofenac with hydrotropes are given in Fig. 2 and 3, respectively. The spectra of aceclofenac shown in Fig. 2 and the mixture of aceclofenac and hydrotropes in Fig. 3 have the same peaks, revealing retention of characteristic bands.

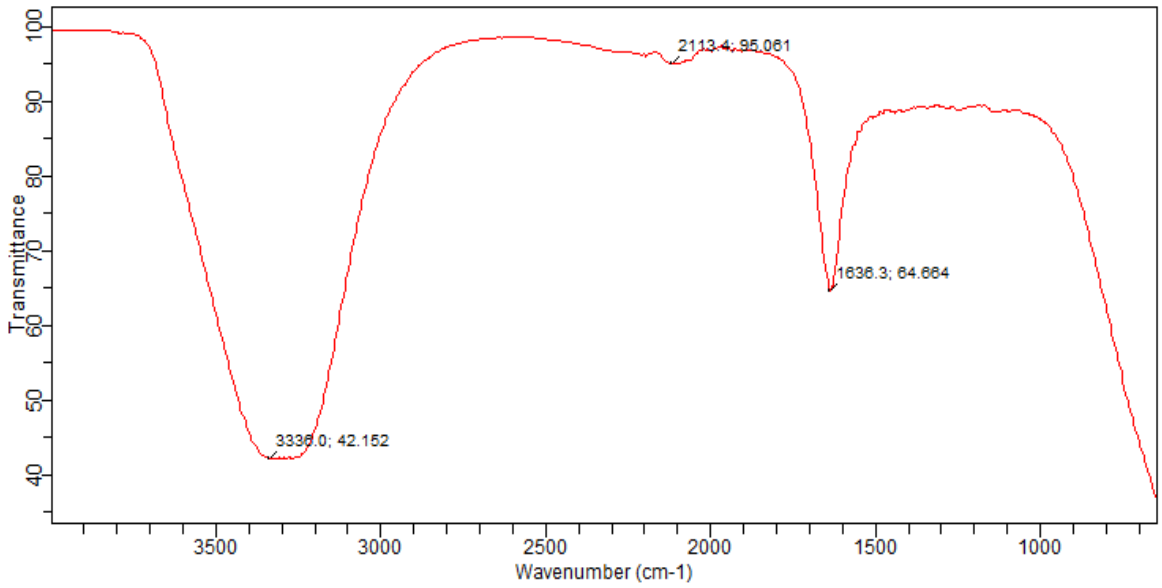


Figure 2: FTIR spectrum of pure aceclofenac

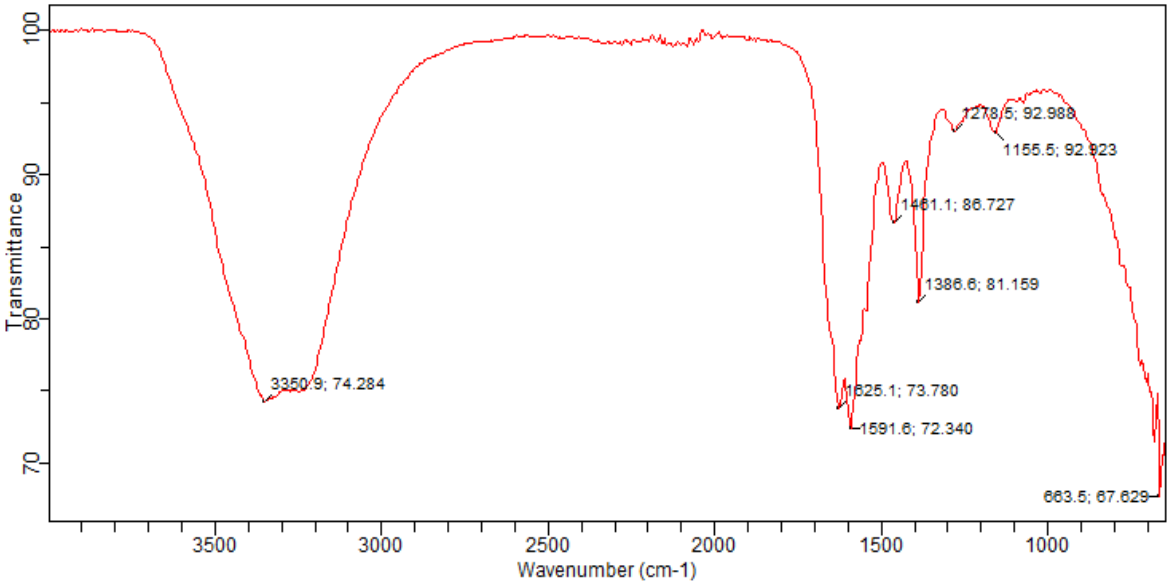


Figure 3: FTIR spectrum of aceclofenac + urea + sodium citrate + sodium benzoate

DISCUSSION

The linearity curve showed that Beer's law was obeyed in the concentration range of 4–24 μg/mL at λ = 273 nm, as shown in Fig 2. This is in line with the study by Garg et al. (2021). The solubilities of aceclofenac considerably improved with the increase in the concentration of the hydrotropes studied, as shown in Tables 2 and 3, which aligns with the study by Kumari et al. (2023). The enhancement of water-solubility by hydrotrope is based on the molecular self-association of hydrotrope and on the association of hydrotrope molecules with the solute. The enhanced solubility effect of the hydrotropes on aceclofenac could be attributed to the following mechanisms of the hydrotropes: self-aggregation, structural making and breaking process, and the ability to form micelle-like structure. Furthermore, Hydrotropic solutions involve a weak van der Waal's interaction between the hydrotropic agent and solute (Patel & Desai, 2023). Hydrotropes contain both hydrophobic and hydrophilic fractions in them. In comparison to surfactant, they contain a very small hydrophobic fraction. The efficiency of hydrotrope solubilization depends on the balance between hydrophobic and hydrophilic parts of hydrotrope. The efficiency of hydrotropic agents when the hydrophobic part of an additive is large and also when the presence of charges on the hydrophilic part is less significant (Vinarov et al., 2018).

The observation of an increase in the solubilization effect of the studied hydrotropes with an increase in concentration is largely due to the self-aggregation potential of the studied hydrotropes because the solubilization power of hydrotropes is governed by their self-aggregation potential (Bolla, 2020). The solubilization of aceclofenac by the studied hydrotropes was also due to a structure-breaker and structure-making process by an electrostatic force of the donor–acceptor molecule, which plays a vital role in the hydrotropic solubilization (Bhalani, et al., 2022). Solutes which are capable of both hydrogen donation and acceptance help to increase solubility. Sodium benzoate, which is an aromatic anionic hydrotrope, may have improved the solubility of aceclofenac via a self-association mechanism and by forming stable mixed micelles, thereby decreasing electrostatic repulsion between the head groups (Munnangi et al 2023).

In addition, urea, sodium citrate and sodium benzoate molecules interact with a less water-soluble molecule via weak Van der Waals interactions such as π–π or attractive dipole–dipole interaction to bring about enhanced solubilization of the sparingly soluble aceclofenac as opined in the findings of (Praveena et al., 2020). The structures of drugs and hydrotropes with different centers of different electronegativity might be responsible for the intermolecular hydrogen bonding and electrostatic attraction (Ibrahim et al., 2020). Hydrogen bonding between the amide group of urea and various negative centers of the drug molecule seems to impact aqueous solubility to aceclofenac. The electronegative carboxylate ion and

hydroxyl group of sodium citrate impact solubility more on aceclofenac (Praveena et al., 2020).

The results in Table 1 revealed that an increase in the concentration of the hydrotropes increased the solubility of aceclofenac, however, this increased level of hydrotrope concentration can lead to toxic effect. Hence, instead of using a single hydrotrope in large concentration as reported by (Patel et al., 2026) for solubilization of aceclofenac. This present study utilized combination of hydrotropes at minimal safe concentrations (1 % w/v) to achieve reasonable increase in solubility and circumvent associated toxic effects of large hydrotrope concentration.

Among the individual hydrotropes studied, sodium citrate (10 % w/v) gave the highest solubilizing effect on aceclofenac with solubility enhancement ratio of 365.80, followed by sodium benzoate, 245.85 and urea 28.81 as shown in Table 1. This gave significant improvement in the solubility of aceclofenac. This is in line with the findings of (Gerald et al., 2024), This report is also in line with the general principle on the solubilizing effect of hydrotropes with an increase in concentration according to (Patel & Desai, 2023). However, this present study also achieved good solubilization of aceclofenac with very low concentration (1% w/v) of the hydrotropes studied, which is preferred for safety and economic reasons. Generally, available data reveal that hydrotropy provides a seamless method for improving the solubility of drugs with poor aqueous solubility.

The results in Table 2 showed that the blend of 6% sodium citrate and 2% sodium benzoate gave a significant solubility enhancement ratio of 288.10 on aceclofenac. The results of the blends of the three hydrotropes at the lowest concentration of 1 % w/v showed improved aqueous solubility of aceclofenac with a solubility enhancement ratio of 102.9 as shown in Table 2. This report satisfies the need for the use of hydrotropes at lowest safe concentration to minimize the toxicities of individual hydrotrope by the application of mixed hydrotropic solubilization at lowest concentration in line with the study by (Gerald et al., 2024) . Similarly, Patel et al. (2026) and El Hamd (2022) opined that synergistic combination of hydrotropic agents can abate the amount of hydrotropic agents employed, thus minimizing the chances of their individual toxicities. The findings reported by Kadam et al., (2016) on the exploration of mixed hydrotropic strategy using etodolac, an insoluble Biopharmaceutical Classification System (BCS) class II drug, corroborates that of this work, as the improvement of etodolac solubility was improved by a fold increase of 274.51 relative to its solubility in distilled water, when blend composition of 10 % sodium benzoate, 5 % sodium acetate and 25% of an undisclosed solvent system was used.

The Thin Layer Chromatography (TLC) study revealed that no interactions or complexation between aceclofenac and the hydrotropes used in line with finding by Sarkar et al., (2022). The solutions of the hydrotropes showed a retardation factor <40%, while drugs samples had a retardation factor > 60%, and there was no new spot/line obtained with the solubilized aceclofenac. The retention factor (Rf) can be used to identify compounds due to their uniqueness to each compound as reported by Kulkarni et al (2020). When comparing two different compounds under the same conditions, the compound with the larger Rf value is less polar because it does not stick to the stationary phase as long as the polar compound, which would have a lower Rf value. Thus, aceclofenac had a higher Rf value than the individual hydrotropes. The results in Table 3 in line with Khan et al., (2021) and Patel et al. (2026), showed no interference of the hydrotrope on aceclofenac.

The FTIR spectra of aceclofenac with urea, sodium benzoate, and sodium citrate showed no interaction, as shown in Figs. 2 and 3.

The spectra of a pure sample of aceclofenac exhibited characteristic peaks corresponding to the functional groups present in each component. The major functional groups present in aceclofenac; O-H (hydroxyl group) stretches (3417.98 cm-1), N-H (amine group) stretches (3325.39 cm-1) and amide carbonyl group C=O stretch band (1636 cm-1) were observed within the absorption frequency even in the presence of the hydrotropes. The absence of any significant shifts or new peaks in the spectra indicates no interaction of aceclofenac with the hydrotropes (urea, sodium benzoate, sodium citrate). This suggests that the components of aceclofenac remain chemically unchanged with respect to the hydrotropes in line with the reported literature (Penjuri et al., 2017).

CONCLUSION

This study has provided strong justification for the possible application of hydrotropes at the lowest, economical, and safest concentrations to improve aqueous solubility of poorly-water soluble aceclofenac. The results of the present study showed that the three hydrotropes investigated at their lowest and safest concentrations enhanced the solubility of aceclofenac. Mixed hydrotropes (urea, sodium citrate and sodium benzoate) at 1% w/v gave an appreciable solubility enhancement ratio of aceclofenac, thus suggesting that mixed hydrotropes is a preferred vehicle for the aqueous solubility enhancement of aceclofenac.

The present study has provided scientific ground for further research into the in vivo bioavailability and anti-inflammatory response study of aceclofenac solubilized with the blends of the studied hydrotropes at their very minimal safe concentration. This will provide insight into the in vitro- in vivo (IVIVC) correlation between the aqueous solubility enhancement of aceclofenac and its improved in vivo bioavailability.

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