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Solubility Enhancement of Ketoprofen and Ibuprofen Using Hydrotropic Solubilization Method

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Abstract- ***Poor aqueous solubility is a major limitation affecting the oral bioavailability of many non-steroidal anti-inflammatory drugs (NSAIDs), particularly ketoprofen and ibuprofen, which belong to the Biopharmaceutics Classification System (BCS) Class II. The present study investigates hydrotropic solubilization as a simple, economical, and scalable approach to enhance the solubility of these poorly water-soluble drugs. Hydrotropic agents such as sodium benzoate, sodium salicylate, and urea were evaluated at varying concentrations (10–40% w/v) using the shake-flask method. Quantitative analysis was performed using UV spectrophotometry, and calibration curves exhibited good linearity, confirming method reliability. Significant enhancement in solubility was observed in hydrotropic solutions compared to distilled water, with higher concentrations producing greater effects. The systems showed good clarity, stability, and drug content within acceptable limits (98–102%), indicating no degradation. The study demonstrates that hydrotropic solubilization is an effective and industrially feasible technique for improving the solubility of ketoprofen and ibuprofen, offering a promising alternative to conventional solubility enhancement methods.***
Keywords- ***Hydrotropic solubilization, Ketoprofen, Ibuprofen, NSAIDs, Solubility enhancement***

I. INTRODUCTION

Poor aqueous solubility remains one of the most intractable problems in oral drug delivery. Current estimates suggest that roughly 40% of existing drug candidates and nearly 70% of molecules in the development pipeline fall into the BCS Class II or Class IV categories, where solubility is the rate-limiting step to absorption [1]. Within this landscape, non-steroidal anti-inflammatory drugs represent a therapeutically critical group that is disproportionately affected. Ketoprofen and ibuprofen are two widely prescribed propionic acid derivatives that belongs to BCS Class II compounds, and their low aqueous solubility translates directly into variable absorption, delayed peak plasma concentration, and inconsistent clinical response, particularly when formulated as conventional solid dosage forms [2][3].

Conventional approaches such as micronization, solid dispersions, and complexation have been used to address solubility issues, yet these methods often involve complex processing or stability concerns. Co-solvency introduces toxicological concerns associated with residual organic solvents [4]. Cyclodextrin complexation, while effective, adds considerable cost and formulation complexity [5]. Nanoparticle-based systems require sophisticated equipment and raise stability concerns during manufacturing and storage [5]. Hydrotropic solubilization offers an alternative by employing high concentrations of hydrotropic agents to increase drug solubility without altering the chemical structure [6].

Hydrotropic solubilization, first described by Neuberg in 1916, operates through an entirely different principle. Hydrotropes are amphiphilic molecules that do not form true micelles but instead self-aggregate at concentrations above a minimum hydrotrope concentration (MHC) into ordered structures that stabilize hydrophobic drug molecules through a combination of hydrophobic interactions, hydrogen bonding, and the Hofmeister salting-in effect [7][8]. The hydrotrope molecules effectively shield the non-polar regions of the drug from water, increasing thermodynamicactivity, and, consequently, apparent solubility. Sodium benzoate, sodium salicylate, urea, and nicotinamide are among the most extensively studied hydrotropes, each with a distinct mechanism and efficacy profile [9].

From a pharmaceutical manufacturing standpoint, hydrotropic systems are attractive for several reasons. They are prepared entirely in water, are free of organic solvents and surfactants, are amenable to scale-up, and the hydrotropes themselves, many of which are GRAS (Generally RecognizedAs Safe) compounds confer no additional toxicological burden [10]. In addition, hydrotropic solutions can serve as intermediary vehicles during wet granulation, enabling the incorporation of poorly soluble drugs into solid dosage forms without the use of co-solvents [11].

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This study investigates the effectiveness of hydrotropic agents in enhancing the solubility of ketoprofen and ibuprofen, with emphasis on simplicity, reproducibility, and industrial applicability.

II. SOLUBILITY PROFILE OF KETOPROFEN AND IBUPROFEN

Ketoprofen and Ibuprofen are common drugs used to reduce pain, inflammation, and fever. However, both of them have poor solubility in water, which creates challenges during drug formulation, especially when preparing liquid dosage forms like syrups or injections. The main reason for their low solubility is their chemical structure. These drugs contain hydrophobic (water-repelling) aromatic rings, which do not interact well with water molecules. In addition, they are weak acids, meaning they do not fully dissolve or ionize in neutral water conditions. Because of this, only a small amount of drug dissolves, which can limit how well it is absorbed in the body [13].

Their solubility depends strongly on pH. In alkaline (basic) conditions, these drugs lose a proton (H^+ ion) and become ionized. The ionized form is more water-soluble, so the drug dissolves better. This is why increasing the pH of the solution can improve solubility.However, adjusting pH is not always practical in real formulations. Very high pH can irritate body tissues or make the drug unstable over time [14]. For example, injections and oral medicines must be within a safe pH range for the human body. Because of these limitations, scientists often look for other methods to improve solubility, such as using solubilizing agents, forming salts, or preparing emulsions [15]. The poor water solubility of ketoprofen and ibuprofen is due to their hydrophobic structure and weak acidic nature. Although solubility increases in alkaline conditions, pH adjustment alone is not always suitable, so alternative formulation techniques are needed [16].Typical aqueous solubility values are in the estimated range of 51 mg/L for Ketoprofen and 21 mg/L for Ibuprofen.These low values restrict the dissolution rate and ultimately delay therapeutic onset. Enhancing solubility without affecting pharmacological activity remains a key challenge.

A. pH-Solubility Relationship

Since both drugs are weak acids, their aqueous solubility is strongly pH dependent. The relationship between ionization and pH is described by the Henderson–Hasselbalch equation. As the pH of the medium increases above the pKa, a greater fraction of the drug exists in the ionized (A^-) form, which is more water-soluble than the unionized (HA) form. Consequently, solubility increases markedly in alkaline environments. At physiological intestinal pH (~7.4), ketoprofen and ibuprofen are predominantly ionized, resulting in significantly higher apparent solubility compared to the acidic gastric environment, where the unionized form predominates. This pH-dependent ionization behavior explains the wide variability in reported aqueous solubility values across different studies and experimental conditions [17].

B. Physicochemical Basis of Poor Solubility

The low aqueous solubility of both drugs is rooted in their molecular architecture. Both ketoprofen and ibuprofen are weak carboxylic acids with pKa values of approximately 4.45 and 4.91, respectively. At physiological gastric pH (1.2–2.0), both molecules exist predominantly in their un-ionised, lipophilic form, which has a much lower aqueous activity coefficient than the ionised species. The high lipophilicity, logP of 3.12 for ketoprofen and 3.97 for ibuprofen, reflects strong intermolecular van der Waals forces and limited hydrogen bond acceptor capacity relative to the drug's non-polar surface area [18][19].

Parameter	Ketoprofen	Ibuprofen
pKa	~4.45	~4.91
Log P	~3.12	~3.97
Solubility	~51 mg/L	~21 mg/L

Table- Solubility Profile of ibuprofen and ketoprofen

At gastric pH, both drugs exist predominantly in unionized form, leading to low solubility. Their hydrophobic aromatic rings further contribute to poor interaction with water molecules.

III. MATERIAL AND METHODOLOGY

A. Materials

Category	Materials

Drugs	Ketoprofen, Ibuprofen
Hydrotropic Agents	Sodium benzoate, Sodium salicylate, Urea
Solvent	Distilled water
Analytical Equipment	UV-Vis spectrophotometer, mechanical orbital shaker, calibrated pH meter, Whatman No. 1 filter paper, 0.45 µm membrane filters

Table- formulation materials for hydrotropic solubilization of ibuprofen and ketoprofen

B. Methodology

The solubility study was carried out using the hydrotropic solubilization technique. Aqueous solutions of hydrotropic agents, namely sodium benzoate, sodium salicylate, and urea, were prepared in distilled water at suitable concentrations. An excess amount of Ketoprofen and Ibuprofen was separately added to each hydrotropic solution to ensure saturation. The mixtures were then subjected to continuous shaking using a mechanical shaker for about 24 hours to attain equilibrium solubility. After shaking, the solutions were allowed to stand and were subsequently filtered to remove any undissolved drug particles. The clear filtrates were analyzed using an appropriate method, such as UV spectrophotometry, to determine the amount of drug dissolved. The solubility of the drugs in hydrotropic solutions was compared with their solubility in distilled water to evaluate the effectiveness of the hydrotropic agents.

1) Solubility Determination (Shake-Flask Method)

a) Sample Preparation

- An excess amount (~200 mg) of Ketoprofen and Ibuprofen was taken separately.
- Each drug was added to 25 mL of different hydrotropic solutions in glass-stoppered conical flasks.

b) Equilibration Process

- The flasks were placed in a mechanical orbital shaker.
- Agitation was carried out at 150 rpm for 24 hours.
- Temperature was maintained at 25 ± 2°C (room temperature).
- Preliminary studies confirmed that 24 hours was sufficient to reach equilibrium solubility.

c) Settling of Suspensions

- After shaking, the flasks were kept undisturbed for 2 hours.
- This allowed undissolved drug particles to settle at the bottom.

d) Filtration

- The supernatant liquid was filtered using Whatman filter paper (No. 1).
- A second filtration was done using a 0.45 µm membrane filter to obtain a clear solution.

e) Dilution of Samples

- The filtrate was diluted appropriately with distilled water.
- Dilution ensured the concentration falls within the linear range of analysis.

f) Spectrophotometric Analysis-

Absorbance was measured using a UV-visible spectrophotometer at:

- 260 nm for ketoprofen
- 222 nm for ibuprofen

g) Calculation of Solubility

Drug concentration was calculated using the respective calibration curve equations.

2) Preparation of Hydrotropic Solutions

Hydrotropic solutions were prepared using analytical grade sodium benzoate, sodium salicylate, and urea. The required amounts of each hydrotropic agent were accurately weighed and dissolved in distilled water to obtain different concentrations, namely 10%, 20%, 30%, and 40% w/v. For instance, a 10% w/v solution was prepared by dissolving 10 g of the hydrotrope in distilled water and making up the volume to 100 mL, while higher concentrations were prepared in a similar manner by proportionally increasing the quantity of solute.

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All solutions were prepared in clean volumetric flasks and mixed thoroughly using a magnetic stirrer to ensure complete dissolution. After complete dissolution, the solutions were allowed to cool to room temperature and were filtered using Whatman filter paper (No. 1) to remove any undissolved particles. The filtered solutions and the pH of each solution were measured using a calibrated digital pH meter and recorded for reference. Freshly prepared solutions were used in all solubility experiments to maintain consistency and accuracy of the results.

C. UV Analysis

UV Spectrophotometry was used for analysis and calibration curve of both drugs were prepared.
Stock solutions (100 µg/mL) were prepared by dissolving accurately weighed quantities of ketoprofen and ibuprofen in respective hydrotropic solutions (30% sodium salicylate for ketoprofen and 30% sodium benzoate for ibuprofen). From these stock solutions, working standards in the range of 2–12 µg/mL were prepared by serial dilution.

IV. EVALUATION

The performance of hydrotropic systems for solubility enhancement of ketoprofen and ibuprofen was assessed using multiple evaluation parameters. These parameters were selected to ensure not only improved solubility but also stability, reproducibility, and suitability for pharmaceutical application.

A. Solubility Enhancement Ratio (SER)

The solubility enhancement ratio (SER) was used as a key parameter to evaluate the efficiency of hydrotropic agents in improving the solubility of Ketoprofen and Ibuprofen. It represents how many times the solubility of a drug increases in the presence of a hydrotropic solution compared to its solubility in distilled water.
Mathematically, SER is expressed as:
$SER = S_{hydrotrope} / S_{water}$
Where:

- $S_{hydrotrope}$ = solubility of the drug in the hydrotropic solution
- S_{water} = solubility of the drug in distilled water

A higher SER value indicates a greater enhancement in solubility, which reflects the effectiveness of the hydrotropic agent. This parameter is useful for comparing different hydrotropes and identifying the most efficient system for solubility improvement.

B. Drug Content Determination

Drug content analysis was carried out to confirm uniformity and to ensure that no degradation occurred during the solubilization process of Ketoprofen and Ibuprofen. The prepared samples were suitably diluted with distilled water and analyzed using a UV spectrophotometer at their respective wavelengths.
The percentage drug content was calculated using the following formula
% Drug Content = 100 x actual drug concentration / theoretical drug concentration
Where:

- Actual Concentration = concentration obtained from experimental analysis
- Theoretical Concentration = expected concentration based on formulation

An acceptable drug content range of 98% to 102% was considered, indicating that the formulation is uniform and free from significant degradation.

C. Clarity and Visual Inspection

Clarity of the hydrotropic solutions was evaluated visually against a black and white background to detect turbidity, precipitation, or phase separation. Clear solutions indicate effective solubilization and absence of undissolved drug particles.

D. Stability Evaluation

Short-term stability studies were conducted to assess physical and chemical stability of the hydrotropic systems over 7 days. Parameters evaluated were Drug content, Precipitation and Color change.

V. RESULTS AND DISCUSSION

A. Solubility Enhancement Study

The solubility of ketoprofen and ibuprofen was determined in distilled water and in different concentrations (10–40% w/v) of hydrotropic agents. A significant increase in solubility was observed with increasing hydrotrope concentration.

Table: Solubility of Ketoprofen in Various Hydrotropic Solutions

Hydrotrope (Conc. % w/v)	Solubility (mg/mL)	SER
Distilled Water	0.051	1.00
Sodium Salicylate 10%	0.210	4.11
Sodium Salicylate 20%	0.395	7.74
Sodium Salicylate 30%	0.610	11.96
Sodium Salicylate 40%	0.825	16.17
Sodium Benzoate 30%	0.480	9.41
Urea 30%	0.310	6.07

Table: Solubility of Ibuprofen in Various Hydrotropic Solutions

Hydrotrope (Conc. % w/v)	Solubility (mg/mL)	SER
Distilled Water	0.021	1.00
Sodium Benzoate 10%	0.140	6.66
Sodium Benzoate 20%	0.290	13.80
Sodium Benzoate 30%	0.470	22.38
Sodium Benzoate 40%	0.690	32.85
Sodium Salicylate 30%	0.420	20.00
Urea 30%	0.260	12.38

The results clearly indicate that solubility increased with hydrotrope concentration. Sodium salicylate produced the highest enhancement for ketoprofen, whereas sodium benzoate showed superior performance for ibuprofen. This difference is attributed to drug–hydrotrope compatibility and intermolecular interactions.

B. Drug Content Determination

Table : Drug Content of Optimized Hydrotropic Formulations

Drug	Hydrotrope Used (30%)	Theoretical Conc. (µg/mL)	Actual Conc. (µg/mL)	% Drug Content
Ketoprofen	Sodium Salicylate	10	9.92	99.2%
Ketoprofen	Sodium Salicylate	10	10.05	100.5%
Ibuprofen	Sodium Benzoate	10	9.88	98.8%
Ibuprofen	Sodium Benzoate	10	10.10	101.0%

All formulations showed drug content within the acceptable limit (98–102%), indicating uniformity and absence of degradation during hydrotropic solubilization.

C. Calibration Curve Results

Calibration curves for both ketoprofen and ibuprofen were constructed using UV spectrophotometric analysis in their respective optimized hydrotropic media. The absorbance of standard solutions (2–12 µg/mL) was measured at 260 nm for ketoprofen and 222 nm for ibuprofen. A linear relationship between concentration and absorbance was observed for both drugs within the studied range, confirming adherence to Beer–Lambert's law.

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Table- Ketoprofen (in 30% sodium salicylate):

Concentration (µg/mL)	Absorbance
2	0.112
4	0.221
6	0.337
8	0.446
10	0.58
12	0.671

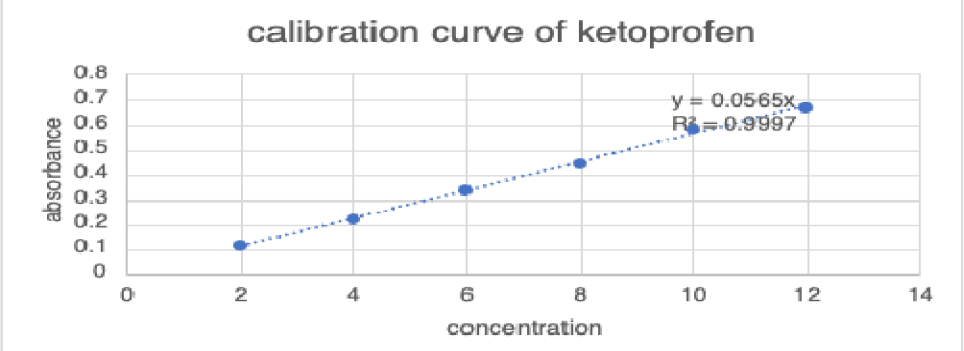


Figure- calibration curve of ketoprofen

Regression equation:
A = 0.0565C + 0.001
Correlation coefficient (R^2): 0.9997

Table- Ibuprofen (in 30% sodium benzoate):

Concentration (µg/mL)	Absorbance
2	0.095
4	0.189
6	0.285
8	0.360
10	0.450
12	0.568

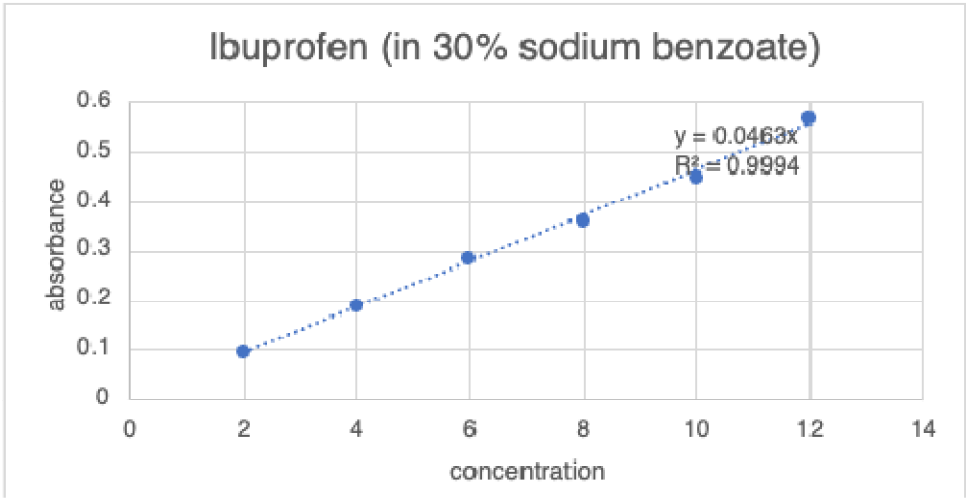


Figure- calibration curve of ibuprofen

Regression equation:
A = 0.0463C + 0.001
Correlation coefficient (R^2): 0.9994
The calibration curves showed excellent linearity, confirming adherence to Beer–Lambert's law. The high R^2 values indicate reliability of the analytical method for drug quantification.

D. Clarity and Visual Inspection

Table : Clarity Evaluation of Hydrotropic Solutions

Drug	Hydrotrope (30%)	Observation
Ketoprofen	Sodium Salicylate	Clear
Ketoprofen	Sodium Benzoate	Clear
Ibuprofen	Sodium Benzoate	Clear
Ibuprofen	Sodium Salicylate	Slight haze

Most formulations were clear, indicating complete solubilization. Slight haze in some systems suggests nearing saturation limits.

E. Stability Studies

Table : Short-Term Stability Data (7 Days)

Drug	Hydrotrope	Day 1 (% Drug Content)	Day 7 (% Drug Content)	Observation
Ketoprofen	Sodium Salicylate	100.2%	99.4%	No significantchange
Ibuprofen	Sodium Benzoate	99.8%	98.9%	No significantchange

No significant variation in drug content or physical appearance was observed over 7 days. This confirms that hydrotropic systems are stable and suitable for formulation purposes.

F. Overall Discussion

The data collectively demonstrate that hydrotropic solubilization significantly enhances the aqueous solubility of ketoprofen and ibuprofen. The enhancement is concentration-dependent and varies with the type of hydrotrope used. Sodium salicylate and sodium benzoate were identified as the most effective hydrotropes for ketoprofen and ibuprofen respectively.
The high solubility enhancement ratios, excellent drug content uniformity, strong linear calibration curves, and good stability profiles confirm that hydrotropy is a reliable, economical, and scalable technique for improving the solubility of poorly water-soluble drugs.

VI. CONCLUSION

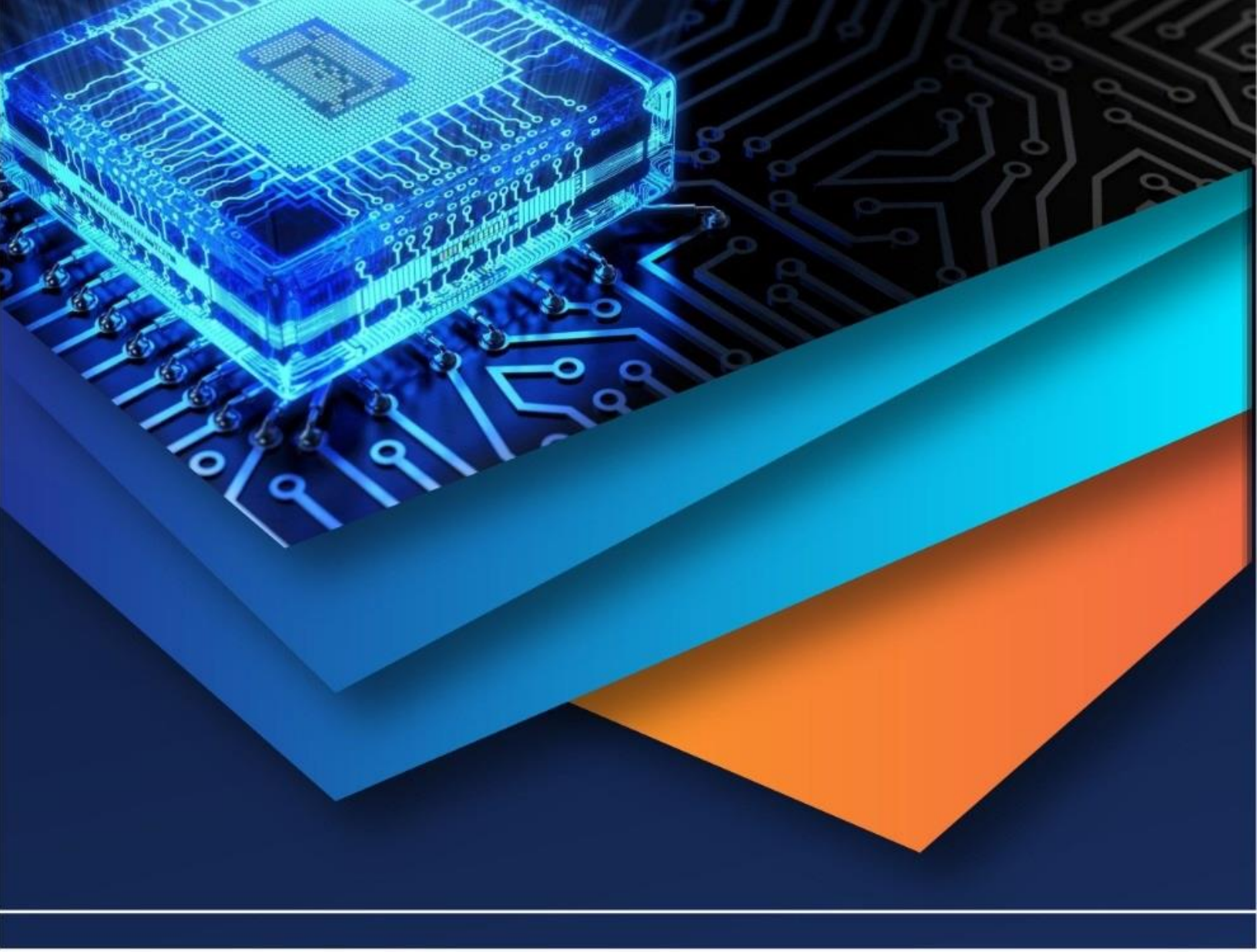
The present study successfully demonstrates that hydrotropic solubilization is an efficient and practical strategy for enhancing the aqueous solubility of the poorly soluble NSAIDs ketoprofen and ibuprofen. The selected hydrotropic agents particularly sodium benzoate (for ibuprofen) and sodium salicylate (for ketoprofen) produced substantial, concentration-dependent solubility enhancement, as evidenced by SER values of up to 32.85 and 16.17, respectively.
The UV spectrophotometric analytical methods demonstrated excellent linearity, precision, and reliability. Drug content analysis confirmed formulation uniformity and the absence of degradation. Clarity and stability studies indicated that optimized hydrotropic systems remained physically and chemically stable over the 7-day evaluation period.
Overall, hydrotropic solubilization offers several manufacturing advantages: simplicity of preparation, avoidance of organic solvents, cost-effectiveness, and straightforward scale-up. The technique holds strong potential for developing liquid and solid dosage forms with improved bioavailability.
The current study was limited to three hydrotropic agents and short-term (7-day) stability under ambient conditions. Future work should include extended stability studies (3–6 months), evaluation of additional hydrotropes such as nicotinamide and sodium citrate, in vitro dissolution profiling from solid dosage forms incorporating these hydrotropic systems, and pharmacokinetic studies to confirm in vivo bioavailability improvement.

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