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Original Article

ENHANCING WATER SOLUBILITY OF A BCS CLASS II DRUG USING HYDROTROPY, MIXED SOLVENCY, COSOLVENCY, AND NANOSUSPENSION TECHNIQUES

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ABSTRACT

Diclofenac sodium, a BCS Class II drug, exhibits high permeability but poor solubility, limiting its bioavailability. This study investigates solubility enhancement techniques like hydrotropy, cosolvency, mix-solvency, and nanosuspension using agents such as urea, sodium acetate, sodium citrate, PEG 400, and glycerin at concentrations of 10–60 PPM. Solubility was evaluated via SHIMADZU UV1800 UV-VIS spectrophotometry. All methods showed a linear increase in solubility, with nanosuspension demonstrating the highest enhancement. The eco-friendly, non-toxic agents used make these techniques suitable for pharmaceutical applications. Overall, the findings support nanosuspension as a promising strategy to improve the bioavailability and therapeutic efficacy of poorly soluble drugs like diclofenac sodium. .

KEYWORDS: Diclofenac sodium, Hydrotropy, Nanosuspension, Co-solvency, Solubility enhancement.

1. Introduction

The most solutes that may dissolve in a certain volume of the solvent are known as soluble. It is defined as the solute in terms of concentration at a saturated concentration at a specific temperature. A qualitative definition of solubility is the spontaneous interaction of two or more substances to produce a homogenous molecular dispersion [1]. Solubility, according to the International Union of Pure and Applied Chemistry, involves the analytical characterization of a saturated solution, typically expressed as the percentage of a specified solute within a particular solvent [2]. A solution is considered saturated when the solute and solvent are in a state of dynamic equilibrium, meaning no additional solute can dissolve under the given conditions. The solubility of a drug or compound can be expressed using various units, including molarity, volume percentage, molar fraction, and other concentration terms, depending on the context and requirements of the analysis [3]. The Indian Pharmacopeia also explains this in terms of the number of solvent components needed for one portion of the solute.

Descriptive term	Parts of Solvent Required for One Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

Fig 1. Expression of solubility according to Indian pharmacopoeia [4]

Additionally, drugs can be categorized into four classes using the Biopharmaceutics Classification System (BCS), which is based on their aqueous

solubility and intestinal membrane permeability. The BCS was developed in the mid-1990s to classify pharmaceutical compounds according to these two key parameters, aiding in the prediction of drug absorption and guiding formulation strategies. [5,6]

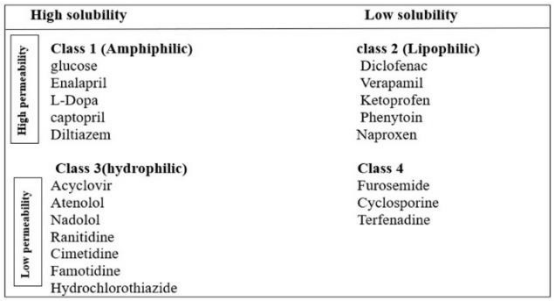

Fig 2. Drugs as per biopharmaceutical classification system.

Several factors can limit the absorption of drugs in the gastrointestinal tract (GIT). Among the most critical are poor membrane permeability and low aqueous solubility of the drug molecules. For an active pharmaceutical ingredient (API) to reach systemic circulation and cross the GIT membranes, it must first dissolve in the gastric or intestinal fluids. Consequently, enhancing the dissolution rate and water solubility of poorly soluble drugs has become a key focus in pharmaceutical research, particularly in efforts aimed at improving the oral bioavailability of active compounds [7,8]. Making the medication available at the right site of action at the ideal dosage is the main goal of the section on future formulation and development.

Solubilization is the process in which the interionic or intermolecular bonds of a solute are disrupted, allowing the solvent molecules to separate and create space for the solute. This is followed by interactions between the solvent and the solute molecules or ions, ultimately leading to the formation of a homogeneous solution[9-11].

Methods used for the improvement of diclofenac sodium solubility in water [12,27].

1.1. Addition of hydrotropic agents

Hydrotropy is a solubilization technique in which the aqueous solubility of a poorly water-soluble drug is enhanced by the addition of a substantial amount of a secondary solute, known as a hydrotropic agent. These agents are typically ionic compounds, such as salts of organic acids combined with alkali or alkaline earth metals. The process increases solubility through a phenomenon referred to as “salting in,” in contrast to “salting out,” where certain salts reduce solubility. Hydrotropic agents may be organic or inorganic, solid or liquid, and are non-micelle forming substances capable of solubilizing otherwise insoluble compounds [13]. The term “hydrotropism” describes the property of certain water-soluble salts, especially those containing bulky cations or anions, to enhance the solubility of nonelectrolytes. The mechanism behind hydrotropy is thought to involve complexation and weak molecular interactions between the drug and hydrotropic agents, facilitated by the presence of numerous molecules in close proximity that promote interaction with the solvent. Common hydrotropic agents include sodium benzoate, sodium acetate, sodium alginate, and urea. These compounds form loose associations with drug molecules, thereby improving their solubility in aqueous media [14].

Hydrotropy refers to the ability of hydrotropic substances to improve poorly soluble substances solubility compounds, such as diclofenac sodium. These agents typically possess both hydrophilic (waterattracting) and hydrophobic (water-repelling) components, which work synergistically to disrupt solutesolvent interactions, thereby increasing solubility. One significant mechanism by which hydrotropic agents achieve this is through the formation of non-covalent complexes with diclofenac sodium, which reduces the intermolecular forces among the drug molecules and enhances its solubility in aqueous solutions. Additionally, certain hydrotropic agents can aggregate in solution to form micelles, effectively encapsulating diclofenac sodium and further increasing its apparent solubility. This micellar formation not only aids in dissolution but also improves the delivery of the drug. Furthermore, hydrotropic agents can reduce the activity coefficient of diclofenac sodium in solution, enhancing the solvent's capacity to solubilize the drug. Another important factor is the alteration of pH by specific hydrotropic agents, which can enhance the ionization of diclofenac sodium. Since the ionized forms of the drug are typically more soluble in water, this pH modification contributes significantly to the overall increase in solubility. Collectively, these mechanisms underscore the potential of hydrotropic agents in enhancing diclofenac sodium's bioavailability and solubility in medication formulations. [15]

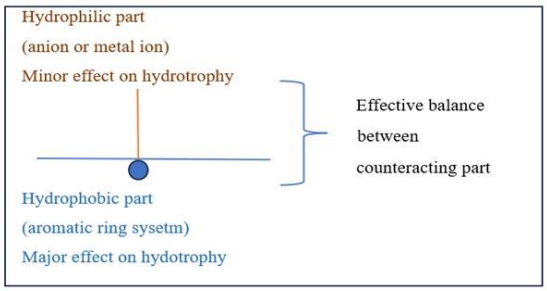

Fig 3. Structure of hydrotropic agents [16].

Hydrotropes offer numerous advantages in pharmaceutical formulations and industrial applications, making them valuable agents for solubilizing hydrophobic compounds. One of their key benefits is their ability to complement other

solubilization techniques, such as salting, micellar solubilization, and miscibility enhancement, due to their independent mode of action as solubilizing agents. This versatility enables hydrotropes to be effectively employed alongside a variety of approaches. A significant advantage of hydrotropy is that it does not require chemical modification of the drug molecule, thereby preserving the chemical integrity of active pharmaceutical ingredients. Furthermore, hydrotropes do not induce temperature changes upon dissolution in water, simplifying processing conditions by eliminating the need for temperature control. The method of application is straightforward, involving only the mixing of the drug with the hydrotrope in an aqueous medium, thus streamlining the formulation process. Unlike other solubilization techniques, hydrotropy does not necessitate the use of organic solvents, complex emulsion systems, or chemical alteration of the drug, making it a more efficient and environmentally friendly alternative. Hydrotropes are typically non-toxic, non-reactive, readily available, and cost-effective, which enhances their suitability for both pharmaceutical and large-scale industrial applications [17].

1.2. Co-solvency

Co-solvency is a solubilization technique that involves the use of one or more miscible liquids, known as co-solvents, to enhance the solubility of poorly water-soluble substances. The addition of co-solvents can significantly improve the solubility, miscibility, and dissolution rate of a drug in a given solution. In some cases, the solubility of a poorly soluble drug has been reported to increase by more than a thousand-fold using co-solvent systems compared to its solubility in water alone. [18]

This method is particularly suitable for highly crystalline compounds with good solubility in solvent mixtures, as well as lipophilic molecules that exhibit poor aqueous solubility. Co-solvents are especially valuable in parenteral formulations due to their low toxicity and effectiveness in solubilizing nonpolar drugs. However, formulations intended for intravenous administration may require dilution with water or aqueous media before delivery to reduce solvent concentration.

Co-solvents can also be combined with other solubilization strategies, such as pH adjustment, to enhance the solubility of weakly soluble compounds. Commonly used low-toxicity co-solvents in pharmaceutical applications include polyethylene glycol (PEG-400), glycerin, ethanol, and propylene glycol. These agents are especially useful for drugs that are poorly soluble in water, offering a practical and effective solubilization strategy. The mechanism by which co-solvents enhance solubility is attributed to their ability to reduce interfacial tension between the hydrophobic solute and the aqueous phase [19]. This process, also known as solvent blending, leverages the molecular structure of co-solvents, which typically feature hydrophobic hydrocarbon regions alongside hydrophilic hydrogen bond donor or acceptor groups. While the hydrophobic regions disrupt the structured hydrogen bonding network of water, thereby reducing cohesive forces, the hydrophilic portions maintain miscibility with water. When a drug is insoluble in water, its solubility can be significantly enhanced by combining it with a water-miscible solvent capable of dissolving the drug. This approach is known as co-solvency, and the solvents used in this method are referred to as co-solvents. Co-solvent systems function by reducing the interfacial tension between the aqueous phase and the hydrophobic solute, thereby facilitating improved solubility. This process is also commonly referred to as solvent blending.

The addition of an organic co-solvent to water can lead to a substantial increase in the solubility of poorly water-soluble drugs. Co-solvents typically possess a small hydrophobic hydrocarbon region and hydrogen bond donor or acceptor groups. The hydrophobic portion of the co-solvent disrupts the hydrogen bonding network of water, reducing the intermolecular cohesive forces, while the hydrophilic groups maintain miscibility with water and contribute to solubility enhancement. Despite the effectiveness of co-solvent systems, the selection of suitable solvents is limited to those that are biocompatible and non-toxic. Commonly used co-solvents include glycerin, N,N-dimethylformamide (DMF), ethanol, propylene glycol, and dimethyl sulfoxide (DMSO). These solvents are frequently employed due to their ability to solubilize a wide range of hydrophobic drugs while maintaining safety for pharmaceutical use [20].

Co-solvents are employed in pharmaceutical formulations to enhance the solubility of poorly water-soluble active pharmaceutical ingredients. The primary co-solvents commonly used in the preparation of various oral formulations include glycerol and polyethylene glycol (PEG). Glycerol, also known as glycerin, is a colorless, odorless, and sweet-tasting liquid that is fully miscible with water. Its co-solvency capability arises from the presence of three hydroxyl (-OH) groups, classifying it as a triol. These hydroxyl groups enable hydrogen bonding with both water and hydrophobic drugs, thereby improving solubility. Glycerol exhibits co-solvency properties similar to ethanol and is frequently used in the preparation of polymer gels. Polyethylene glycol (PEG) is a polymer consisting of repeating ethylene oxide units. The general chemical structure is denoted as $HO\text{-}(CH_2CH_2O)_n\text{-}H$, where *n* represents the number of repeating units. The physical properties of PEG, such as viscosity and solubility, are dependent on its molecular weight. PEG 200 and PEG 400, due to their relatively low molecular weights and liquid physical state, are particularly preferred as co-solvents in pharmaceutical solutions. [21].

The mechanism of co-solvency involves a combination of physicochemical interactions that collectively enhance the solubility of solutes in solvent systems. One of the fundamental mechanisms is polarity modification, wherein co-solvents alter the overall polarity of the solvent mixture. For example, the addition of a nonpolar cosolvent to a polar solvent can decrease the system's overall polarity, thereby increasing the solubility of nonpolar solutes. In addition to polarity adjustment, co-solvents can engage in hydrogen bonding with both the solute and the primary solvent. These interactions help stabilize the solute within the solution, further improving solubility. Another significant factor is the disruption of the solvent structure. Co-solvents can interfere with the structured hydrogen-bonding network commonly observed in polar solvents like water, thereby facilitating the integration of solute molecules into the solvent matrix. Moreover, co-solvents can alter the dielectric constant of the solvent mixture, influencing the solvation energy required for ionic and polar solutes. A decrease in dielectric constant can favour the dissolution of less polar compounds, while a moderate dielectric environment can promote the solubility of amphiphilic substances. Entropy changes also contribute to the cosolvency effect. The introduction and mixing of co-solvents often increase system entropy, which thermodynamically favors solute dissolution. Collectively, these mechanisms illustrate the multifaceted nature of co-solvency and emphasize its potential as a powerful strategy in pharmaceutical and chemical formulations for improving the solubility of poorly soluble compounds [24].

1.3. Mix solvency*:*

Hydrotropic solubilization shares similarities with co-solvency and is considered a manifestation of the mixed solvency concept. According to this concept, all substances possess inherent solubilizing potential, and any soluble material—whether in the form of a solid, liquid, or gas—can enhance the solubility of poorly water-soluble drugs. In a solubility enhancement study using salicylic acid (a model drug known for its poor aqueous solubility), solubility tests were carried out using various solubilizing agents. These included co-solvents such as glycerin, propylene glycol, PEG 300, and PEG 400; hydrotropic agents like urea and sodium citrate; and water-soluble solids such as PEG 4000 and PEG 6000. The tests were performed both individually and in ten randomly formulated blends composed of solubilizers from the aforementioned categories, maintaining a constant total concentration of 40% w/v. The results demonstrated that seven out of ten combinations exhibited a synergistic enhancement of solubility, confirming the potential effectiveness of the mixed solvency approach for improving the aqueous solubility of poorly soluble drugs [22].

Mixed solvency enhances solubility through multiple mechanisms involving interactions between different solvents. A central aspect of this approach is the synergistic effect observed when various solvents interact not only with the solute but also with each other. This interaction can result in solubility enhancement that surpasses the sum of the individual effects of each solvent. By combining solvents of varying polarities and hydrogen-bonding capacities, the solvation environment is optimized, allowing for more effective interaction with the solute. This tailored environment improves the dissolution of compounds, particularly those that are poorly soluble in water. Additionally, the process of solvent mixing leads to an increase in system entropy, which thermodynamically favours the dissolution of solutes by enhancing the overall free energy change of the system. Mixed solvency also contributes to the disruption of structured hydrogen-bonding networks present in primary solvents such as water, enabling easier incorporation of solute molecules into the solution. Moreover, modification of the dielectric constant of the solvent mixture plays a crucial role in solubilizing ionic and polar compounds by influencing solvation dynamics [23].

1.4. Nano suspension:

This method is employed for drugs that exhibit poor solubility in both water and oil. Nanosuspensions are biphasic systems consisting of nanosized drug particles dispersed in an aqueous medium, stabilized by suitable surfactants. These formulations are particularly beneficial for enhancing the bioavailability of poorly soluble drugs intended for oral, pulmonary, parenteral, and topical administration. The particle size distribution in nanosuspensions is generally below 1 micron, with the average particle size typically ranging between 200–600 nm. This nanosizing significantly increases the surface area of the drug particles, improving dissolution rates and absorption. Nanosuspension technology has been successfully applied to various poorly soluble drugs, including buparvaquone, amphotericin B, paclitaxel, atovaquone, and tarazepide. Common techniques utilized for the preparation of nanosuspensions include Nanocrystals, DissoCubes, Nanopores, and Nanoedge technologies, each offering specific advantages in particle size reduction and stability enhancement [25,26].

2. Materials and methods

The experimental study was conducted using a variety of laboratory instruments and chemicals to ensure accurate and reproducible results. A Shimadzu UV-1800 UV-Visible spectrophotometer was employed for the spectral analysis of samples, while an aczet ultrasonic homogenizer was used to achieve uniform dispersion of components. An analytical weighing balance facilitated the precise measurement of chemical substances. The chemicals utilized in the

study included distilled water, diclofenac sodium, urea, sodium acetate, sodium citrate, polyethylene glycol (PEG-400), and glycerin. Various laboratory apparatus such as volumetric flasks, spatulas, beakers, and magnetic stirrers were employed for the preparation and thorough mixing of solutions. A stock solution of diclofenac sodium was prepared by dissolving 10 mg of the drug in 100 mL of distilled water, resulting in a 100 ppm solution. From this stock, serial dilutions were prepared to obtain concentrations of 10, 20, 30, 40, 50, and 60 ppm by mixing 1, 2, 3, 4, 5, and 6 mL of the stock solution, respectively, with distilled water to make up a final volume of 10 mL in each case. The required volume of stock solution was accurately measured using a pipette and transferred to a clean graduated cylinder or volumetric flask, followed by the addition of distilled water. Each solution was thoroughly mixed using a magnetic stirrer to ensure homogeneity. The prepared dilutions were then stored in properly labelled volumetric flasks at room temperature for 2 hours and marked with their respective concentrations and date of preparation. This procedure was consistently followed for all subsequent blends of diclofenac sodium to ensure uniformity across different concentrations.

Content Of Blends:

Table 1. Blends for the addition of hydrotropic agents

Sr. No.	Blend preparation
1	10 mg Diclofenac sodium + 10 mg urea
2	10 mg Diclofenac sodium + 10 mg sodium acetate
3	10 mg Diclofenac sodium + 10 mg sodium citrate
4	10 mg Diclofenac sodium + 10 mg urea + 10 mg sodium acetate

Table 2. Blends for addition of cosolvents

Sr. No.	Blend preparation
1	Diclofenac +1 ml PEG 400
2	Diclofenac + 1 ml glycerin
3	Diclofenac +1 ml PEG 400 +1 ml glycerin

Table 3. Blends for mix-solvency

Sr. No.	Blend preparation
1	10 mg Diclofenac + 5 mg Sodium Citrate + 1 ml PEG 400
2	10 mg Diclofenac + 5 mg Sodium Citrate + 1 ml glycerin
3	10mg Diclofenac + 5 mg urea + 5 mg sodium acetate + 5 mg sodium citrate + 1 mL PEG 400

Table 4. Parameter criteria for the homogenizer.

Sr. No.	Parameters	Set at
1	Process time	0h 5m 0s
2	On the pulse	2.0 seconds
3	Pulse off	2.0 seconds
4	Alarm temperature	50^0 c
5	Probe temperature	31^0 c
6	Program no	1@ 6
7	Power rate	70%

Preparation of Nano suspension:

1. Make the Solution of 10mg of Diclofenac in Distilled Water of 100 mL

2. Make 100 mL of the Stock Solution.

3. Make the Dilution of 30, 40, 50 & 60 ppm wisely.

4. Set the parameters in the homogenizer accordingly.

3. Results and discussion

Spectra of diclofenac sodium

Initially, the UV spectrum of diclofenac sodium was recorded to determine its maximum absorption wavelength (λ_{max}), which was found to be 276 nm. This wavelength was subsequently used for the analysis of all parameters throughout the study.

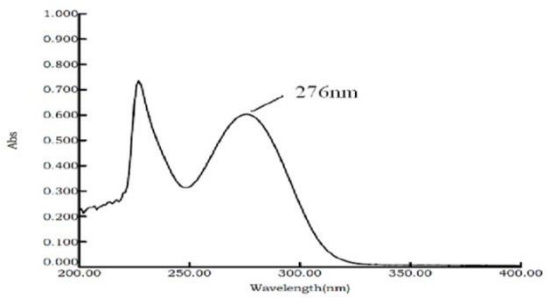

Fig 4. UV spectrum of diclofenac sodium

3.1. Addition of Hydrotropic Agents

Table 5. Addition of urea to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac +urea
1	10 ppm	0.266	0.310
2	20 ppm	0.535	0.548
3	30 ppm	0.803	0.817
4	40 ppm	1.075	1.138
5	50 ppm	1.415	1.459
6	60 ppm	1.650	1.754

Table 6. Addition of sodium acetate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + sodium acetate
1.	10 ppm	0.266	0.303
2.	20 ppm	0.535	0.618
3.	30 ppm	0.803	0.876
4.	40 ppm	1.075	1.148
5.	50 ppm	1.415	1.489
6.	60 ppm	1.650	1.804

Table 7. Addition of sodium citrate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + sodium citrate
1	10 ppm	0.266	0.311
2	20 ppm	0.535	0.684
3	30 ppm	0.803	0.898
4	40 ppm	1.075	1.259
5	50 ppm	1.415	1.554
6	60 ppm	1.650	1.849

Table 8. Addition of urea & sodium acetate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac +urea+ sodium acetate
1	10 ppm	0.266	0.402
2	20 ppm	0.535	0.714
3	30 ppm	0.803	0.925
4	40 ppm	1.075	1.298
5	50 ppm	1.415	1.633
6	60 ppm	1.650	1.895

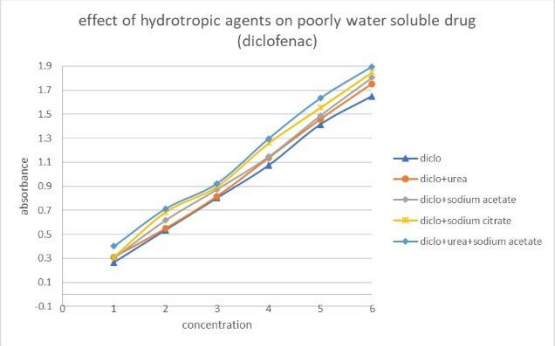

Fig 5. Effect of hydrotropic agent on diclofenac sodium.

According to the results, the incorporation of hydrotropic agents—particularly sodium citrate, sodium acetate, and urea—significantly enhanced the solubility of poorly water-soluble substances. This improvement was demonstrated by increased absorbance values, indicating that the use of these agents is an effective strategy for enhancing drug solubility and, consequently, improving bioavailability.

3.2. Addition of Co-Solvents

Table 9. Addition of glycerin to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + glycerin
1	10 ppm	0.266	0.295
2	20 ppm	0.535	0.543
3	30 ppm	0.803	0.828
4	40 ppm	1.075	1.136
5	50 ppm	1.415	1.438
6	60 ppm	1.650	1.819

Table 10. Addition of PEG 400 to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + PEG 400
1	10 ppm	0.266	0.346
2	20 ppm	0.535	0.651
3	30 ppm	0.803	0.951
4	40 ppm	1.075	1.260
5	50 ppm	1.415	1.563
6	60 ppm	1.650	1.884

Table 11. Addition of PEG 400 and glycerin to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + PEG 400+glycerin
1	10 ppm	0.266	0.382
2	20 ppm	0.535	0.699
3	30 ppm	0.803	0.993
4	40 ppm	1.075	1.287
5	50 ppm	1.415	1.604
6	60 ppm	1.650	1.948

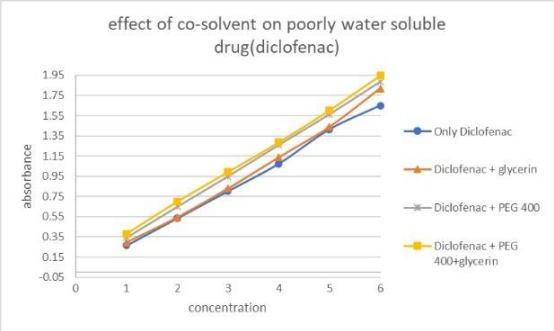

Fig 6. Effect of cosolvent on diclofenac sodium.

The incorporation of co-solvents such as glycerin and PEG 400 significantly enhances the aqueous solubility of diclofenac sodium, as demonstrated by increased absorbance values. This improvement underscores the potential of co-solvency as an effective strategy for developing improved drug delivery systems, which may contribute to enhanced therapeutic efficacy and better patient outcomes for formulations containing diclofenac sodium.

3.3. Addition of Mix-Solvents

Table 12. Addition of glycerin and sodium citrate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + glycerin + sodium citrate
1	10 ppm	0.266	0.330
2	20 ppm	0.535	0.618
3	30 ppm	0.803	0.964
4	40 ppm	1.075	1.243
5	50 ppm	1.415	1.553
6	60 ppm	1.650	1.819

Table 13. Addition of PEG 400 and sodium citrate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + PEG 400 +Sodium Citrate
1	10 ppm	0.266	0.384
2	20 ppm	0.535	0.682
3	30 ppm	0.803	0.996
4	40 ppm	1.075	1.358
5	50 ppm	1.415	1.701
6	60 ppm	1.650	1.920

Table 14. Addition of PEG 400, sodium citrate and sodium acetate to diclofenac

Sr. No.	Concentration	Only Diclofenac	Diclofenac + PEG 400 +Sodium Citrate +sodium acetate
1	10 ppm	0.266	0.466
2	20 ppm	0.535	0.742
3	30 ppm	0.803	1.059
4	40 ppm	1.075	1.448
5	50 ppm	1.415	1.758
6	60 ppm	1.650	2.165

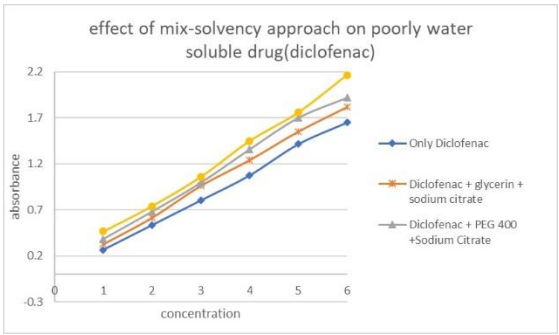

Fig 7. Effect of mix-solvency on diclofenac sodium.

The application of mixed solvency, utilizing agents such as urea, sodium acetate, sodium citrate, PEG 400, and glycerin, significantly enhances the solubility of diclofenac sodium, as evidenced by increased absorbance measurements. This innovative approach demonstrates strong potential for the development of more effective drug delivery systems, ultimately improving the therapeutic efficacy of diclofenac sodium.

3.4. Nanosuspension

Table 15. Nanosuspension of different concentration.

Sr. No.	Concentration	Only Diclofenac	Nanosuspension
1	10 ppm	0.266	0.389
2	20 ppm	0.535	0.757
3	30 ppm	0.803	1.088
4	40 ppm	1.075	1.383
5	50 ppm	1.415	2.332
6	60 ppm	1.650	2.454

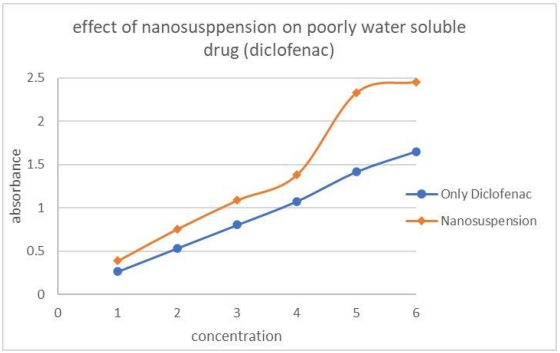

Fig 8. Effect of nanosuspension on diclofenac sodium.

The application of the nanosuspension technique has demonstrated a significant enhancement in the solubility of diclofenac sodium, as reflected by increased absorbance measurements. This innovative approach not only improves the drug's solubility but also presents substantial potential for the development of more efficient drug delivery systems. Ultimately, such advancements may lead to improved therapeutic efficacy, better patient outcomes, and broader clinical applications for diclofenac sodium.

4. Limitations and Future Directions

Despite the promising results, this study has certain limitations. The solubility enhancement was evaluated only through in vitro spectrophotometric analysis, and no in vivo studies were conducted to confirm improved bioavailability. Furthermore, the study utilized a limited set of solubilizing agents and concentration ranges, which may not capture the full potential of each technique. The nanosuspension system, while effective, was not assessed for long-term physical or chemical stability. Future research should include pharmacokinetic studies to validate bioavailability enhancement, expand the scope of solubilizing agents and concentrations, and investigate formulation stability and scalability for industrial application.

5. Conclusion

This research successfully demonstrated the potential of multiple strategies like hydrotropy, co-solvency, mixed solvency, and nanosuspension for enhancing the water solubility of poorly soluble drugs. All four techniques showed a consistent and measurable increase in solubility, as indicated by elevated absorbance values. Among them, nanosuspension proved to be the most effective approach, primarily due to its ability to reduce particle size and increase surface area, thereby significantly improving solubility. These results highlight the promising role of solubility enhancement techniques in increasing the bioavailability of insoluble drugs. The study offers valuable insights for the development of more efficient drug delivery systems and sets the groundwork for future pharmaceutical innovations aimed at improving therapeutic efficacy and patient outcomes.

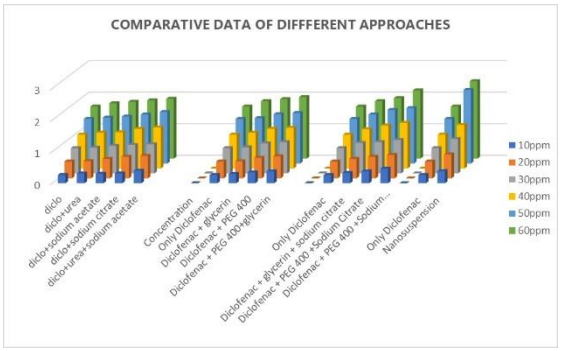

Fig 9. Comparison of all techniques of solubility enhancement on diclofenac sodium.

Author Contributions: Vijayraj N. Sonawane: Conceptualization, Original Draft; Dhanashree I. Wagh: Data Collection, Analysis; Sakshi P. Bhamare: Visualization, Supervision; Khemchand R. Surana: Writing, Project Administration; Deepak D. Sonawane: Funding Acquisition, Resources; Sunil K. Mahajan: Review, Editing. All authors have read and agreed to the published version of the manuscript.

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