Improving Aceclofenac Solubility through Advanced Crystallization Methods

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Abstract*— Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with limited water solubility, leading to challenges in its formulation for therapeutic use. In this study, we explored the application of antisolvent crystallization as a method to enhance the solubility of aceclofenac. The antisolvent crystallization technique involves the addition of a non-solvent to the solvent containing the drug, promoting the precipitation of fine crystals with improved solubility properties. Our experiments focused on optimizing the process parameters such as solvent-to-antisolvent ratio, stirring rate, temperature, and concentration of aceclofenac solution. We utilized scanning electron microscopy (SEM) to analyze and characterize the crystal structure, morphology, and thermal properties of the aceclofenac crystals produced. The results demonstrated a significant enhancement in the solubility of aceclofenac through antisolvent crystallization. The optimized conditions yielded fine crystals with increased surface area and improved dissolution rates compared to the untreated drug. These findings suggest the potential of antisolvent crystallization as a promising strategy for enhancing the solubility and bioavailability of poorly soluble drugs like aceclofenac, helping to create pharmaceutical formulations that are more effective.

Index Terms*— Solubility, Aceclofenac, Crystallization, Dissolution.

I. INTRODUCTION

The greatest solute that may dissolve in a specific volume of solvent is known as solubility. It may be described in qualitative and quantitative terms. It is exactly defined quantitatively as the concentration of the solute in a saturated solution at a specific temperature. The natural propensity of two or more compounds to combine into a homogenous molecular combination is referred to as solubility [1].

Drug solubility, which takes into consideration factors like temperature, pH, and pressure, is the greatest concentration at which the drug solute may dissolve in a particular solvent. The dissolving rate of a medicine is a variable attribute that is more closely linked to the pace at which the drug becomes accessible for absorption in the body than the solubility of the drug in a saturated solution, which is a fixed feature. An extensive list of ions and how they behave with other ions—that is, whether they precipitate or remain aqueous—are provided by a solubility chart. In order for the pharmacological response to occur, the medication must be soluble in order to reach the proper bloodstream concentration.

Since it affects the drug's release, absorption, rate of dissolution, and ultimately its bioavailability, the solubility of the substance is an important property. Processing is therefore necessary to improve the drug's water solubility and dissolution [3].

II. MATERIALS AND METHODS

Materials

aceclofenac received as gift sample from wockhardt research Centre Aurangabad, ethanol and acetone obtained standard deviation (SD) Variety Traders, Amravati, Maharashtra. distilled water is collected in P.R. Pote Patil College of Pharmacy, Amravati.

Methods

Antisolvent method

Three solvent systems and an antisolvent were used in the antisolvent crystallization process to create the aceclofenac crystal. Ethanol and acetone were selected as the solvents, while water was used as an antisolvent. In a beaker, 100 mg of aceclofenac was dissolved in 5 milliliters of ethanol or acetone. In addition, water is added to another beaker as an anti-solvent. Drop by drop, the clear aceclofenac solution combination is introduced to the antisolvent-filled beaker until precipitations happen. After letting the mixture stand for ten minutes, Whatmann filter paper is used to filter

the mixture. For a whole day, the gathered powder is dried at 37.5°C [4].

Crystallization under ultrasonication in antisolvent.
Aceclofenac crystal was created using the antisolvent crystallization process and ultrasonication. A system of solvents and antisolvents was engaged. Water was used as the anti-solvent and ethanol and acetone as the solvents. Aceclofenac (100 mg) was dissolved in 5 milliliters of ethanol or acetone. The translucent aceclofenac solution was added dropwise to a beaker with antisolvent (10 ml water). Ultrasonication was used to apply ultrasound energy right away, lasting five minutes at 50% power and nine duty cycles. Filter the solution after sonication, then allow it to air dry at room temperature [5].

Evaluation of pure drug and prepared crystals
Solubility studies
A 10 ml volumetric flask containing distilled water, 0.1N HCl (pH 1.2), or phosphate buffer solution (pH 6.8) was filled with the excess drug or crystals that were formed during sonocrystallization. The volumetric flasks were shaken at room temperature for 48 hours at 100 revolutions per minute on a rotary shaker. After 48 hours, the combination was filtered, the filtrate was appropriately diluted, and an ultraviolet (UV)-visible spectrophotometer (UV-Lab India) was used to examine the results at 275 nm [5].
In vitro drug release studies

The eight station dissolving test equipment (Nucleus Bioscience, India) with a paddle speed of 50 rpm was used to conduct the in vitro drug dissolution investigation of pure drug or crystals. The 900 ml dissolution media was made up of either phosphate buffer solution (pH 6.8) or 0.1N HCl (pH 1.2). An aliquot was taken out and replaced with new media at predefined intervals. Using an appropriate blank, the amount of medication dissolved in each aliquot was determined at 275 nm using a UV-visible spectrophotometer (UV-Lab India) [6].

Solubility studies by using UV-spectrophotometer.
10 mg of pure aceclofenac drug and prepared crystals were dissolved in 100 ml of solvent to make a stock solution with a concentration of 100 micrograms/ml. 1 ml was then taken from the stock solution and added to a 10 ml volumetric flask, resulting in a concentration of 10 micrograms/ml. Dilutions were made to achieve concentrations of 2, 4, 6, 8, 10, and 12 micrograms/ml. These solutions were analyzed at 275 nm using a UV-visible spectrophotometer.

Scanning electron microscopy
The drug samples and the prepared crystals underwent sputter coating with an electrically conducting metal like gold. This process coated the drug and crystals, enabling their shape and surface topography to be examined using SEM (BIOWIZARD 4.1 SOFTWARE).

III. RESULT AND DISCUSSION

Evaluation of drug and prepared crystals at different temperature

The solubility study of aceclofenac in various solvents, including distilled water, 0.1N HCl, and phosphate buffer solution (pH 6.8), is presented in Figure 2. The results indicate that the solubility of aceclofenac in distilled water, 0.1N HCl, and phosphate buffer solution (pH 6.8) was found to be 0.003±0.00145 mg/ml, 0.0780±0.877 mg/ml, and 0.1097±0.0699 mg/ml, respectively. These findings highlight the significantly lower solubility of aceclofenac in water compared to 0.1N HCl and phosphate buffer solution.

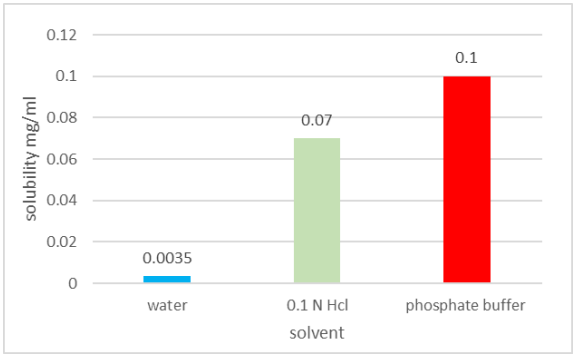


Fig 1. Comparison of solubility of aceclofenac in distilled water,

0.1 N Hcl, and phosphate buffer solution.

In vitro drug release studies
The dissolution characteristics of pure aceclofenac and prepared crystals were investigated across varying temperatures using distilled water as the dissolution

medium. Figure 2 displays the in vitro dissolution profile data for crystals E, E US, A, and A US. These findings mirror those observed for bath sonicator crystals prepared using ethanol as the solvent and bath sonication, which exhibited the highest solubility.

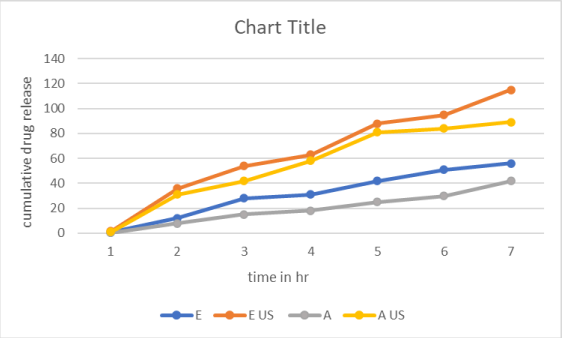


Fig 2. Comparison of In Vitro Dissolution Characteristics of Diverse Crystals Formed via Bath Sonicator.

Assessment of crystals created with a bath sonicator (Nucleus Bioscience).

The solubility data for the prepared crystals are presented in Figure 3. Crystals E exhibited a solubility of 1.44 mg/ml in distilled water, while sonication (using a bath sonicator) increased the solubility of E US to 1.96±0.017 mg/ml. Crystals A demonstrated a solubility of 0.99±0.062 mg/ml in distilled water, whereas sonication (A US) resulted in a solubility of 1.826±0.020 mg/ml. Notably, the solubility of crystals prepared in ethanol and acetone showcased a significant enhancement due to the sonication process, highlighting the impactful role of sonication, particularly when utilizing a bath sonicator, in altering the solubility profiles of the prepared crystals, as depicted in Figure 3.

Table 1. crystal prepared by ultrasonication at 25℃ ±1℃

Formulations	Solubility in water mg/ml
E	1.44
A	0.99
E U S	1.96
A U S	1.82

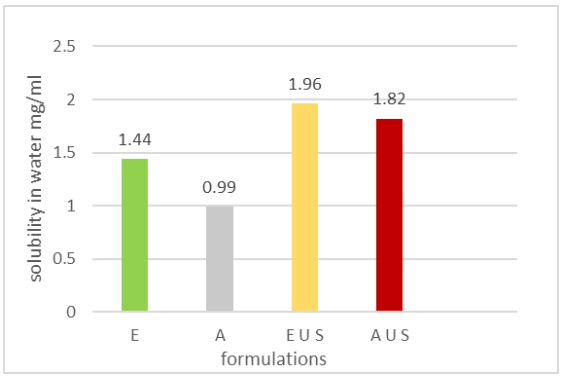


Fig 3. Comparison of solubility study profile of different prepared crystal by bath sonication.

The conclusion drawn from the above results is that "After sonication, the crystals exhibited significantly increased solubility in ethanol, demonstrating the efficacy of the sonication process in enhancing solubility."

Evaluation of pure drug and crystals prepared in ethanol solvent after sonication (by using UV-spectrophotometer).

Table 2. Absorbance of pure drug and prepared crystals Using ethanol as solvent after sonication

Concentration mg/ml	Abs of PD	Concentration mg/ml	Abs of C EUS
2	0.122	2	0.217
4	0.214	4	0.432
6	0.321	6	0.666
8	0.424	8	0.855
10	0.512	10	1.074
12	0.62	12	1.321

PD - Pure drug (aceclofenac)

C E US – Crystals prepared using ethanol after sonication

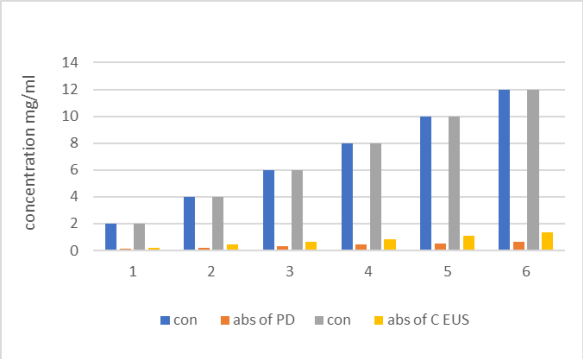


Fig 4. Comparison of solubility study profile of pure drug and prepared crystals using ethanol after sonication.

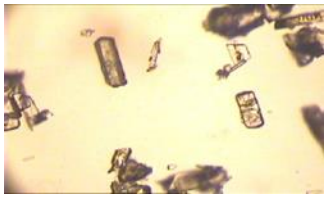
Conclusion the advanced crystallization technique employed in this study has demonstrated significant improvements in the solubility of aceclofenac. The preparation of crystals using antisolvent crystallization has shown enhanced dissolution behavior compared to pure aceclofenac. The calibration curve analysis of pure drug and crystals further confirmed the solubility enhancement achieved through this method. These findings suggest promising implications for the development of gel formulations with improved drug delivery properties. Future studies could explore optimizing the crystallization parameters for enhanced solubility and investigate the application of these crystals in various pharmaceutical formulations.

Characterization of drug and prepared crystals

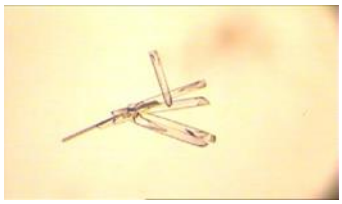
Scanning electronic microscopy

SEM micrographs of aceclofenac and the prepared crystals are depicted in Fig 5.The application of ultrasonic power resulted in a reduction in particle size, attributed to the homogenization of the mixture comprising the antisolvent (water) and the primary solution (acetone or ethanol). Ultrasonication facilitated a more uniform distribution of supersaturation, thereby preventing localized nucleation outbreaks. Moreover, ultrasonic irradiation expedited the formation of crystal nuclei. The morphology of aceclofenac significantly improved post-ultrasonic crystallization, yielding crystals considerably smaller than those of the pure drug [6].

Sample A



Sample B



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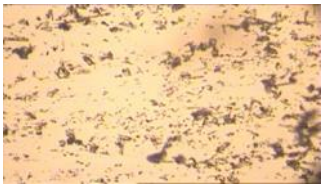
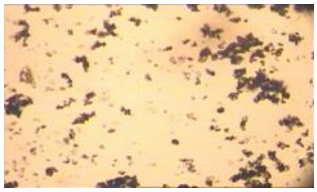


Sample D



Sample E

Fig 5. Scanning electron microscopy

A - pure drug

B- crystals prepared using ethanol

C- crystals prepared using acetone

D- crystals made by sonication in ethanol

E- crystals made by sonicating them in acetone

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