



Micronization Techniques for Solubility Enhancement of Aceclofenac as a potential Solubility Enhancement Approach

Vishal Gupta^{1*}, Sokindra Kumar², Rajesh Agrawal³

^{1,2}Faculty of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram Delhi-Haridwar Meerut Bypass Road, NH-58, Meerut-250005 & Sr. Research Scientist – Formulation Development, Modi-Mundipharma R&D Centre, Modipuram, Meerut, India-250110

²Faculty of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram Delhi-Haridwar Meerut Bypass Road, NH-58, Meerut-250005

³GM – R&D, Modi-Mundipharma R&D Centre, Modipuram, Meerut-250110

***Corresponding author:** Vishal Gupta

Faculty of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram Delhi-Haridwar Meerut Bypass Road, NH-58, Meerut-250005 & Sr. Research Scientist Formulation Development, Modi-Mundipharma R&D Centre, Modipuram, Meerut, India-250110

Email address: vishal@modimundipharmaplant.com Tel: 91 9411817303

History: Article

Submitted: 15 June 2023

Revised: 10 July 2023

Accepted: 5 August 2023

Published: August 2023

CC License

CC-BY-NC-SA 4.0

Abstract:

Aceclofenac is a BCS class II poorly aqueous soluble drug that has significant oral bioavailability limitations after intake. Numerous solubility enhancement techniques are available for the solubility enhancement, out of various techniques Micronization is simple, quick and an effective technique for solubility enhancement. The aim of present research work is use Micronization Technique for solubility enhancement. Micronization technique increases the solubility of Pure Aceclofenac through increasing particle surface area. Aceclofenac material is micronized by Air Jet mill to produces materials of below 25µm size ranges. This micronized Aceclofenac material further characterized for physical property and aqueous solubility determinations.

Micronization technique reduces crystallinity of pure Aceclofenac material by increasing their surface area and exhibited increase in dissolution of micronized Aceclofenac as compared to Pure Aceclofenac. Various characterization techniques (DSC, XRD & SEM) also reveal that Aceclofenac crystallinity is significantly minimized due to either conversion of crystalline compound in to amorphous form or reduction of particle size to its molecular level.

KEYWORDS: Micronization Technique, Solubility Enhancement, Poorly Aqueous Soluble, BCS Class, Aceclofenac

INTRODUCTION

Oral dosage forms are the most popular forms among all dosage forms due to the advantages of being easy to prepare, easy intake, cost-effective, and showing flexibility to form dosage forms. If a drug is administered orally, it goes to the biological system including dissolution in gastrointestinal fluids, permeation across the cell membrane and follows first-pass metabolism to finally reach its site of action in the systemic circulation. Dissolution is as main aspect to increase the bioavailability of the drug. Nowadays solubility of poorly soluble drugs present ongoing challenges with their translation into viable medicinal products^{1, 2}.

Solubility is defined as the ability of molecules to dissolve in an aqueous medium. Solubility plays a major role in increasing the therapeutic index of the dosage form. The Biopharmaceutical classification system (BCS) involves the determination of solubility and permeability of drugs under some specified conditions. BCS class was first introducing in year 1995 by Amidon and his co-workers. Its classification is based on key parameters like permeability, dissolution, and solubility, which help to control the absorption of the drug. BCS class are classified into four types according to permeability and solubility of drugs³⁻⁵. (Figure 1).

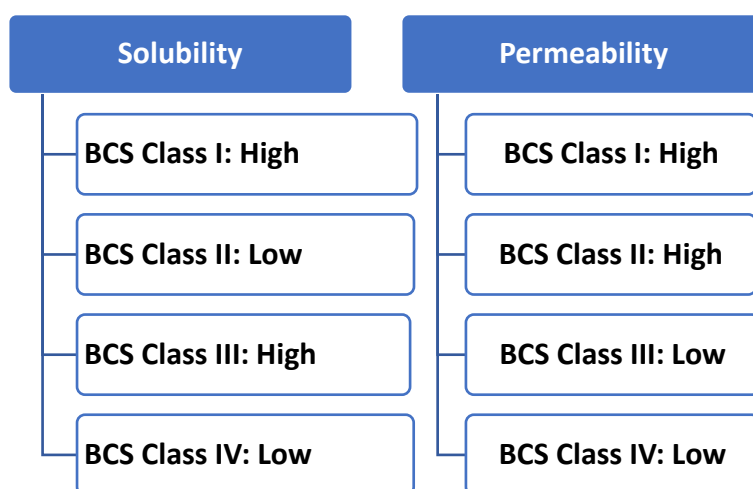


Figure 1: BCS classification of Drugs

Aceclofenac is an anti-inflammatory, analgesic and BCS class II, non-steroidal anti-inflammatory (NSAID) drugs. It needs modification in drug property due to its poor aqueous solubility⁶. The main object of current research work is to improve aqueous solubility of Aceclofenac (poorly water-soluble drugs) formulation containing Aceclofenac API by Micronization. Micronization technique enhances the solubility by producing fine or micronized materials which have enhanced surface area⁷⁻¹². The prepared micronized API has characteristics enhance aqueous solubility and ultimately enhanced bioavailability due to conversions of amorphous Aceclofenac or increased surface area of crystalline Aceclofenac or pure Aceclofenac.

MATERIALS AND METHODS

Materials

Aceclofenac sample was procured from M/s SaralChemtech LLP, India as a gift sample. All other ingredients and chemicals were of analytical grade.

Methods

Particle Size Distribution characterization of Pure Aceclofenac

Aceclofenac Particle size distribution was characterized by Malvern Mastersizer 2000 Instrument (M/s Malvern Panalytical Ltd, United Kingdom). Malvern Mastersizer 2000 uses laser diffraction to measure particle size distribution of a powdered material by wet dispersion method. A very small quantity of (~50mg) sample is needed for Malvern Particle size distribution analysis and results can be recorded within 10 minutes.

Micronization (Spiral Air jet Mill) as a Solubility Enhancement Technique

Micronization is conventional technique for the particle size reduction, which reduces particles up to the micrometer size. Micronization increases the dissolution rate of drugs through increasing particle surface area, accelerating dissolution rates and ultimately improves the bioavailability of poorly soluble APIs⁸⁻¹³.

Air Jet Mill's was used for grinding of a crystalline Pure Aceclofenac (ACL), to reduced particle size from micrometer to nanometer range and classify them in a very narrow range particle size at a same time. The Aceclofenac powder was slowly feed into a flat circular, enclosed collision milling chamber through a venture. In this milling chamber, a stream of moisture free compressed air was introduced in vortex motion at a specific pressure (2 bar) along with feed material, leading to causes rapid particle-to-particle collisions with regular impaction and abrasion on the particles in fast motion and thereby reduction in the particle size takes place due to high velocity of air. The fine particles are carried up stack into the particle classifier. Particle classification is made by inertia, the larger particles due to their inertia continue through the down stack and re-enter the milling chamber for further grinding and fine powder are collected in collector assembly⁸⁻¹⁹ (Figure -2).



Figure 2: Air Jet Mill for Micronization of Powder

Comparative Characterization and Evaluation of Micronized Aceclofenac (ACLM)

a) Particle Size distribution of Aceclofenac by Malvern Mastersizer 2000

Particle size distribution of Pure Aceclofenac and Micronized Aceclofenac were determined by Malvern Master sizer 2000. Air Jet Mill's reduced particle size of Aceclofenac from micrometer to nanometer range.

b) Theoretical yield (%)

Theoretical Yield of Micronized Aceclofenac was estimated after Micronization²⁰⁻²³. The percent Theoretical yield was calculated by using following formula:

$$\% \text{ Theoretical Yield} = \frac{\text{Practical Weight (Weight after micronization)}}{\text{Theoretical Weight (Total weight before micronization)}} \times 100$$

c) Saturation Solubility Study

Saturation Solubility study was carried out in purified water. For this study, excess amount (containing 100 mg drug) of sample were added in 25 ml Stoppard conical flask containing purified water as a dissolution medium and agitated continuously at room temperature for 24 hours on shaker (RPM 50). The samples were kept overnight for equilibrium and filtered through whatman filter (grade 41). Each filtrate was suitably diluted with dissolution medium (purified water) and amount of drug dissolve was estimated [In triplicate] Spectrophotometrically at 275 nm lamda max.

d) Bulk & Tapped Density Study

Bulk Density was determined as per United State Pharmacopeia (USP) method²⁴ by pouring the known amount of drug in a graduated cylinder and compared with pure Aceclofenac. Tapped density was also determined by pouring the known amount of drug in a graduated cylinder and cylinder was tapped for a fixed distanced (300 mm) for sufficient time as described in USP. Bulk & tapped density are determined by following equations:

Bulk Density (g/ml) = Weight of mass (g)/ Volume occupy by powder as such (ml)

Tapped Density (g/ml) = Weight of mass (g)/ Volume occupy by powder after tapping (ml)

Available online at: <https://jazindia.com>

e) Compressibility Index (CI %) & Hausner Ratio(HR)

It is a way for the measurement of flow property of materials. The Hausner ratio is an indirect measurement of the property of a bulk material to reduce its volume under mechanical influence. It is also a measure of the ability to compress and of the interaction between the particles. A lower compressibility or a lower Hausner ratio of a material indicates better flow properties²⁴. Both CI & HR are determined by using bulk density & tapped density as per method described in pre-formulation section.

f) Flow Property Study

Powder flow has very importance in a pharmaceutical manufacturing process. The blending process is terrible, if a powder has low flowability resulting poor content uniformity in dosage forms. Flow property of selected solid dispersion was determined by fixed funnel method as described United State Pharmacopeia (USP)²⁵ and compared with pure Aceclofenac & Micronized Aceclofenac.

g) Solid State Characterization

The crystal structure of pure Aceclofenac(ACL) and micronized Aceclofenac (ACLM) was confirmed by DSC, FT-IR and XRD studies²⁰⁻²³.

Differential Scanning Calorimetry (DSC)

The thermal behaviour of pure Aceclofenac and micronized Aceclofenac selected solid dispersion formulations were studied by Differential Scanning Calorimeter (DSC, DSC 822® Software STAR® 16.10, Mettler). In this study, different samples were heated at 10°C/min over a temperature range of 40-250°C under flow of nitrogen (60ml/min) in pierced aluminium pans and crystallinity of Aceclofenac was compared with prepared solid dispersions²⁰⁻²³.

Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectroscopy was carried out on FT-IR spectrophotometer (FT-IR Spectrophotometer, Perkin Elmer, Spectrum RX1, USA). The spectrum was recorded between 4000 -400cm⁻¹. The FT-IR spectra of the different samples were compared with pure Aceclofenac spectra²⁰⁻²³.

X-Ray Diffraction (X-RD)

The powder X-Ray diffraction pattern was determined on selected batches of solid dispersion using Multipurpose Versatile XRD System (Model-SmartLab 3kw; make-Rigaku Instruments) to characterize the physical form of Aceclofenac. The sample was spread on the glass slide (approximate 0.5 mm thickness). The prepared slide was further inserted vertically at 0° angle in the X-ray diffractometer. The results were recorded over a range of 0-90° (2θ) using Cu-target X-ray tube and Xe-filled detector. The operating conditions were as per following: voltage 40kv, current 20mA, scanning speed- 1/min, Detector-Scintillation counted, Sample Holder-Non-rotation at Room Temperature²⁰⁻²³.

h) Microscopic Study

The Aceclofenac (ACL) and Micronized Aceclofenac (ACLM) were microscopically analysed to check shape, surface appearance, color, transparency and crystalline nature of API. Approximately 5 to 10 mg of sample was taken on a cleaned glass slide, kept on a microscopic plate and analyzed by a Digital microscope with Digieye 330 and Digieye 510 Camera at magnification of 40x and recorded digitally (color photo camera, Dewinter, India) using Dewinter Biowizard software ver. 4.5.

i) Scanning Electron Microscopy (SEM)

Scanning electron microscopy is used to study surface characteristics of material. The surface characteristics of the selected solid dispersion were studied by using High resolution Emission Scanning Electron Microscope with EDS (FE-SEM; JEOL, JSM-76100PLUS fine coat ion sputter, Tokyo, Japan) instrument. The photomicrographs were taken at an excitation voltage of 20 kV with 1000x magnification and their surface characteristics were compared with pure Aceclofenac²⁰⁻²³.

j) In-Vitro Dissolution Study

The In-vitro dissolution study of pure Aceclofenac (ALC) and Micronized Aceclofenac (ACLM) were performed in 7.5 pH phosphate buffer at 50 RMP using USP II apparatus (Sotex India) at 37°C±0.5°C. At a predetermined time intervals up to 120 minutes (10 min, 20 min, 30 min, 45 min, 60 min, 90min and 120 min), 10 ml of dissolution medium was withdrawn, filtered through Whatman filter (grade 41). Each filtrate

was suitably diluted (5 ml with 25 ml) with dissolution medium (phosphate buffer pH 7.5) and amount of drug dissolve was estimated Spectrophotometrically at 275 nm lamda max at each time points. The dissolution experiment was performed in six set of vessels (n=6). The maximum drug release of micronized Aceclofenac was compared with pure Aceclofenac²⁶.

RESULT AND DISCUSSIONS

Characterization and comparative evaluation of Micronized Aceclofenac (ACLM)

a) Particle Size Distribution of Aceclofenac & micronized Aceclofenac

Malvern report confirms that pure Aceclofenac has more than 100 μm particle size as such. Whereas, Micronization by jet mill produces particle size below 25 μm . The Malvern particle size distribution of pure Aceclofenac (ACL) & micronized Aceclofenac (ACLM) are summarized below in Table 1. A comparative Graph of particle size distribution was represented in figure 3.

Table1: Particle Size distribution of Pure Aceclofenac (ACL) & Micronized Aceclofenac (ACLM)

S.No.	Manufacturer/ Supplier: Saral Chemtech LLP., India			
	[B.No. SCT/ACF/409/22-23]			
	Material name	d(0.1) μm	d(0.5) μm	d(0.9) μm
1.	Pure Aceclofenac (ACL)	12.651	40.273	108.054
2.	Micronized Aceclofenac (ACLM)	2.679	6.695	22.033

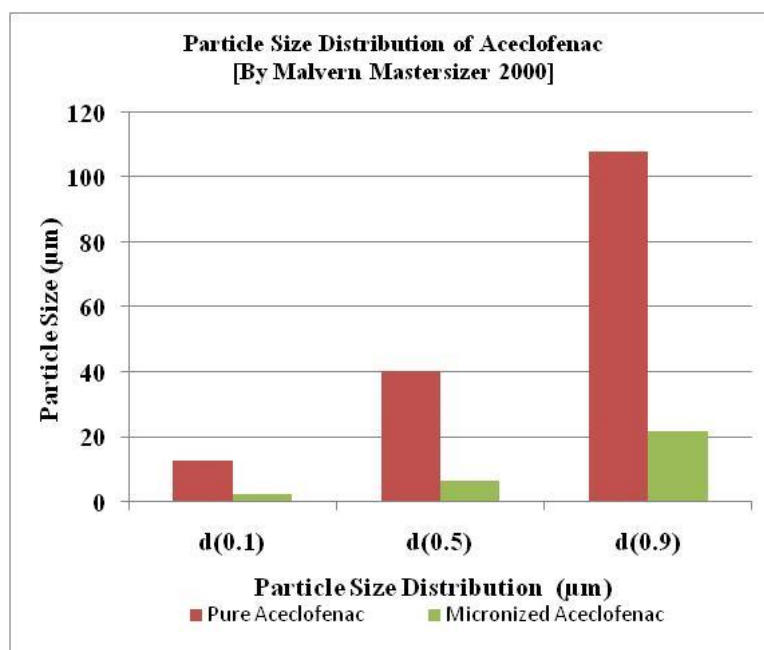


Figure3: Particle size distribution of Pure Aceclofenac (ACL) & Micronized Aceclofenac (ACLM)

b) Practical yield (%)

The % practical Yield of Micronized Aceclofenac was found around $90.2\% \pm 0.77$ due to its losses during Micronization process.

c) Saturation Solubility Study

Saturation Solubility study of pure Aceclofenac (ACL) and micronized Aceclofenac (ACLM) were carried out in purified water at 25°C temperature. The micronized Aceclofenac solubility was found around 0.135 ± 0.02 mg/ml as compared to pure Aceclofenac solubility 0.056 ± 0.01 mg/ml, this indicates that

Micronization increase the aqueous solubility of material. Figure 4 graphically presented solubility data of selected pure & micronized Aceclofenac.

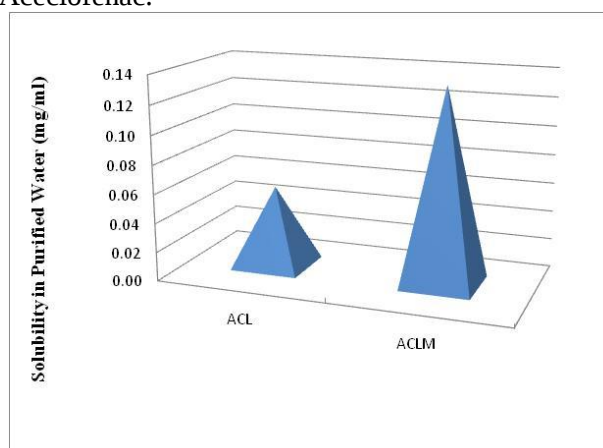


Figure 4: Solubility of Aceclofenac in Purified Water

d) Bulk & Tapped Density Study

The Bulk density and tapped density values of pure Aceclofenac and Micronized Aceclofenac were observed in a range on 0.122 g/ml to 0.444 g/ml. The minimum bulk density was found in micronized Aceclofenac indicates that material is lighter or fluffy in nature and has poor flow property. Compressibility Index (CI %) & Hausner Ratio (HR) can also be determined during the measurement of density analysis. All these are an indirect method to determine flow property of material. All the data were represented in Table2.

Table 2: Bulk density, tapped density, Compressibility Index, Hausner ratio and Flow characteristics of Pure Aceclofenac (ACL) and Micronized Aceclofenac (ACLM).

Sample Code	Bulk Density (g/ml) Mean $\pm$ SD (n=3)	Tapped Density (g/ml) Mean $\pm$ SD (n=3)	Compressibility Index (CI) (%) Mean $\pm$ SD (n=3)	Hausner Ratio (HR) Mean $\pm$ SD (n=3)	Flow Character
ACL	0.313 $\pm$ 0.1	0.444 $\pm$ 0.1	29.69 $\pm$ 0.1	1.422 $\pm$ 0.2	Poor
ACLM	0.122 $\pm$ 0.1	0.250 $\pm$ 0.1	51.22 $\pm$ 0.2	2.050 $\pm$ 0.6	Very Poor

e) Flow Property Study by Angle of Repose

Pure Aceclofenac and micronized Aceclofenac were determined by fixed funnel method. Pure Aceclofenac & micronized Aceclofenac found high angle of repose value around $46.23^\circ \pm 0.15$ & $64.68^\circ \pm 1.22$ respectively. This indicates that micronized Aceclofenac has very poor flow property and difficult to handle during manufacturing of dosage form. Angle of Reposes is graphically represented in figure5.

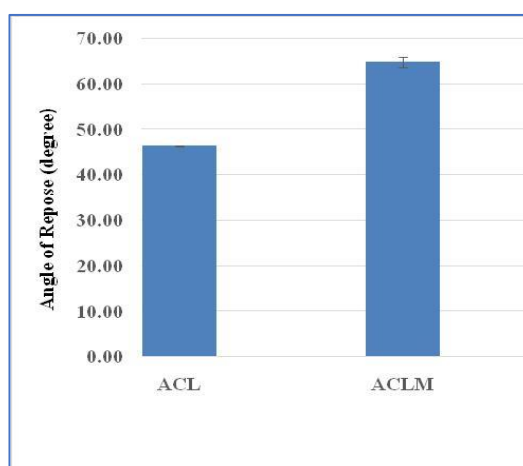


Figure 5: Angle of Reposes data of Aceclofenac (Pure & Micronized)

f) In-Vitro Dissolution Study

The In-Vitro dissolution profile (n=6) of pure Aceclofenac (ALC) and Micronized Aceclofenac (ACLM) were examined over a period of 120 minutes at 50 RMP, USP II apparatus (Sotex India) in 7.5 pH phosphate buffer with powder equivalent to 200 mg of Aceclofenac at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ are depicted in figure 6. It is clearly observed that the rate of dissolution of pure Aceclofenac is only $44.5\% \pm 6.0$ in 60 minutes whereas micronized Aceclofenac shows $73.0\% \pm 1.4$. It is also indicated that and micronized Aceclofenac has increased in-vitro drug dissolution $19.5\% \pm 1.3$ in first 10 minutes as compared to pure Aceclofenac (only $3.2\% \pm 0.4$).

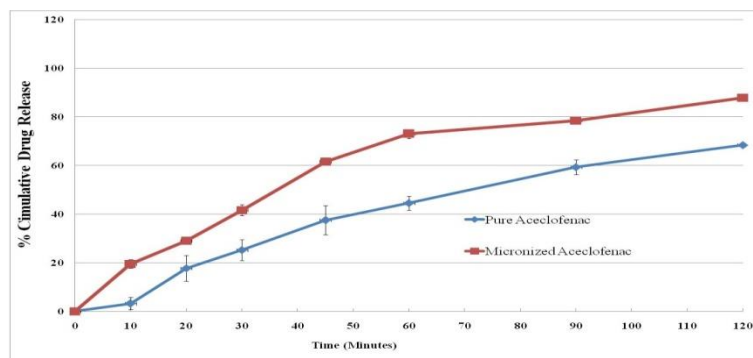


Figure 6: In-Vitro dissolution of Aceclofenac with respect to time.

6) Release Kinetic Study

Release kinetics of micronized Aceclofenac (ACLM) was compared with pure Aceclofenac kinetics. Various kinetic models and reactions are analysed such as Zero Order, first order, Higuchi model, Korsmeyer Peppas model and Hixson Crowell model. Release kinetic study (R^2 Value) of Pure Aceclofenac and Micronized Aceclofenac) are shown in Table 3 and figure 7 & figure 8 respectively.

Table 3: Release Kinetic Study data of Aceclofenac

Sample Code	Release Kinetics (R^2 Value)				
	Zero Order	First Order	Higuchi	KorsmeyerPeppas	Hixson Crowell
ACL	0.9550	0.9953	0.9510	0.9451	0.9874
ACLM	0.8738	0.9799	0.9671	0.9585	0.9562

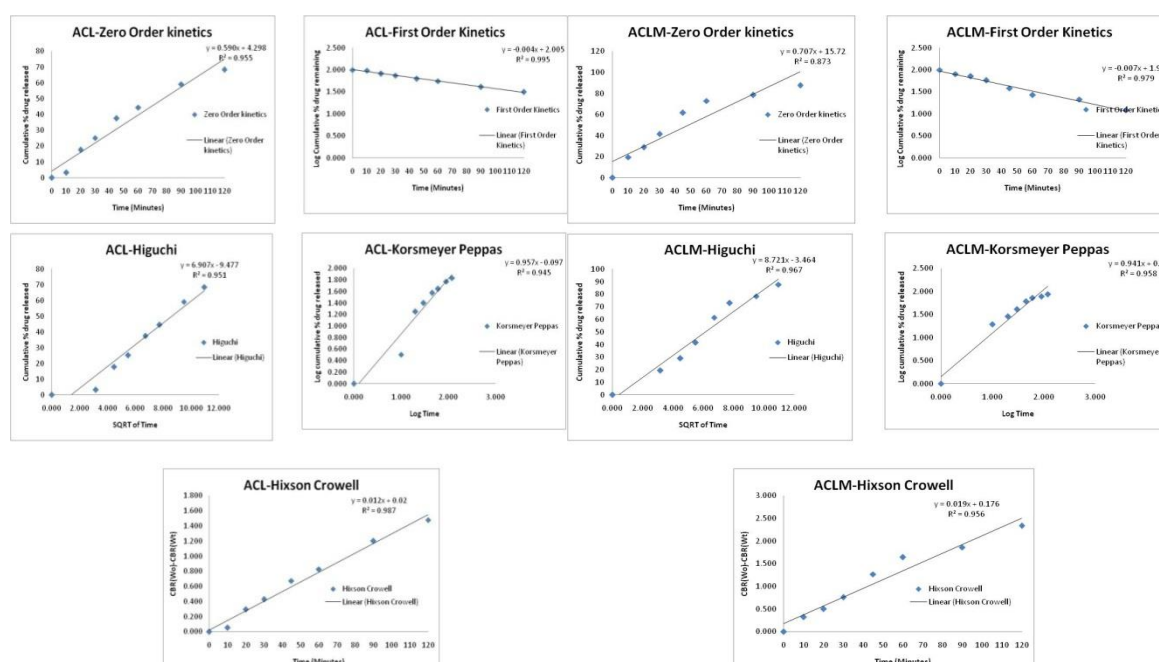


Figure 7: Release Kinetic of ACL

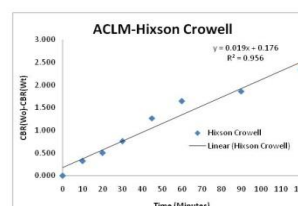


Figure 8: Release Kinetic of ACLM

h) Solid State Characterization

Differential Scanning Calorimetry (DSC)

The overlay Differential Scanning Calorimetric (DSC) thermogram of pure Aceclofenac and micronized Aceclofenac are shown in figure 9. A sharp endothermic peak is observed in pure Aceclofenac and micronized Aceclofenac at 153.19°C & at 153.57°C respectively analogous to its melting point. Whereas a peak intensity is decreased in micronized Aceclofenac corresponding pure Aceclofenac.

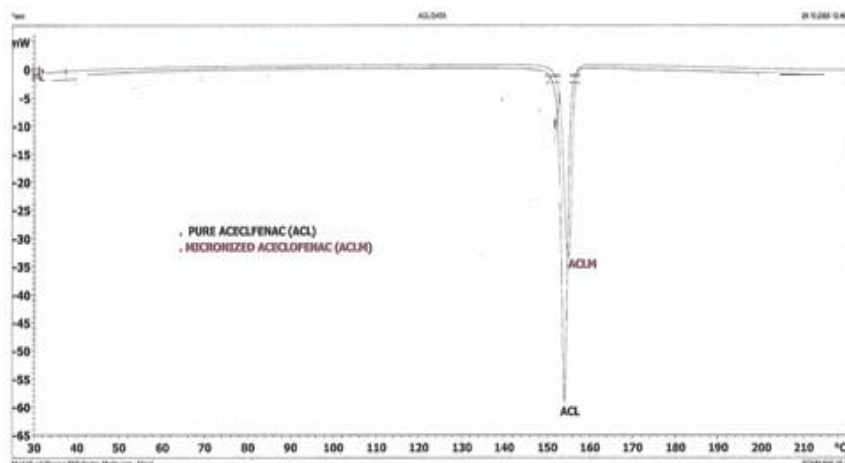
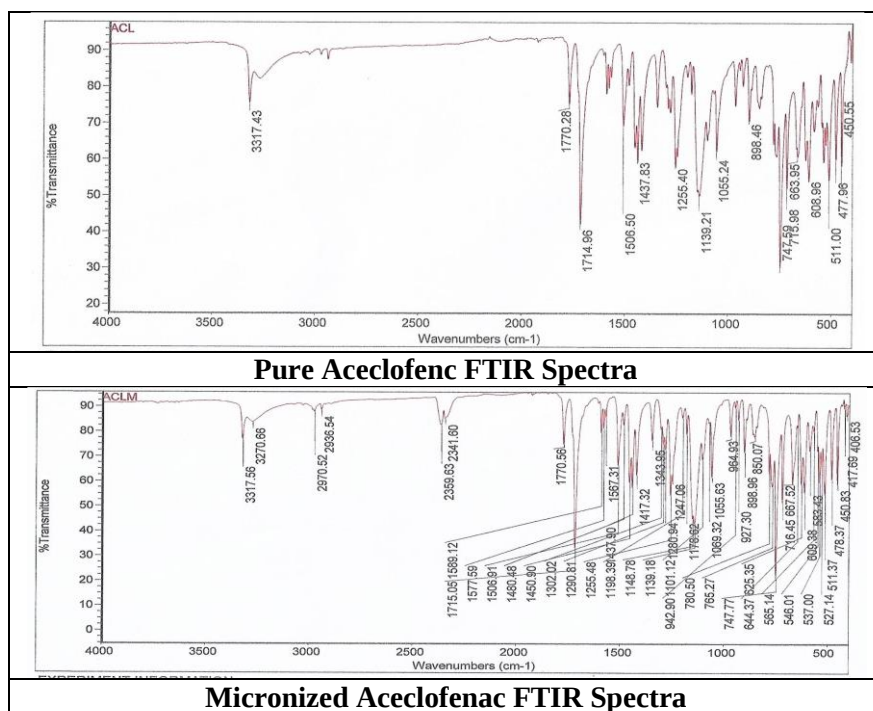


Figure 9: An overlay DSC thermogram of Pure Aceclofenac (ACL) and Micronized Aceclofenac (ACLM)

Fourier Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectra of pure Aceclofenac and micronized Aceclofenac (figure 10) showed sharp characteristics carboxylic hydroxyl group peak attributed at 3317 cm⁻¹, secondary amine peak at 3270 cm⁻¹, two ketone bond peak at 1770 cm⁻¹ & 1715 cm⁻¹ and Moderate to prominent phenyl ring bands at 1588.98, 1506.64, 1450.65, 1280.73, 1148.65, 942.85, 747.61, 536.85 cm⁻¹.

Hence, FT-IR spectra reveals that there is NO incompatibility between drug-polymer physical mixture & solid dispersion methods.



X-Ray Diffraction (X-RD)

XRD scan of Pure Aceclofenac (ACL) and Micronized Aceclofenac (ACLM) are shown in figure 11. The XRD spectra of pure Aceclofenac and micronized Aceclofenac illustrated strong and sharp peak at diffraction angle(2θ) of about 17° , 22° , 25° & 26° with intensity of more than 60 lakhs counts, suggested that well defined crystal structure of Aceclofenac.

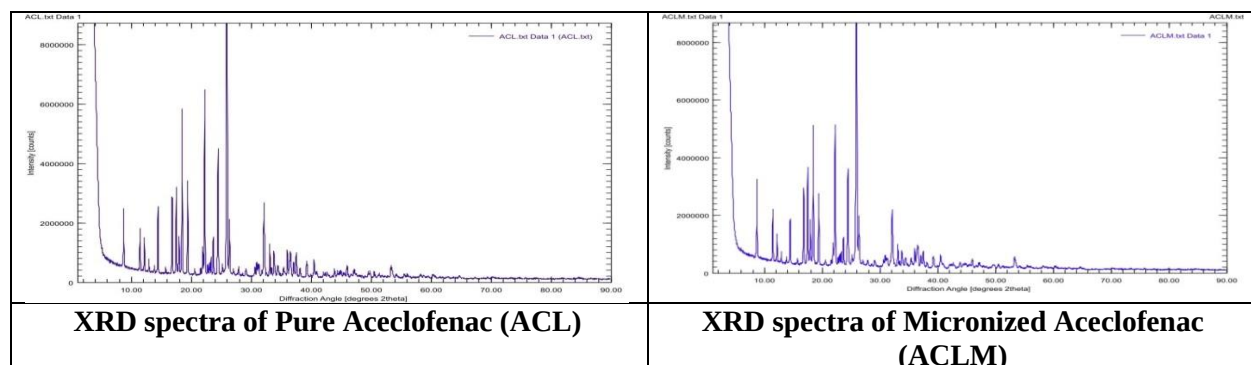


Figure 11: XRD spectra of Aceclofenac and Micronized Aceclofenac) Microscopic Study

The Aceclofenac (ACL) and Micronized Aceclofenac (ACLM) were microscopically analysed to check shape, surface appearance, color, transparency and crystalline nature of API. Microscopic study reveals that Pure Aceclofenac has well defined large crystalline structure whereas micronized has very fine irregular shape crystals (figure 12).

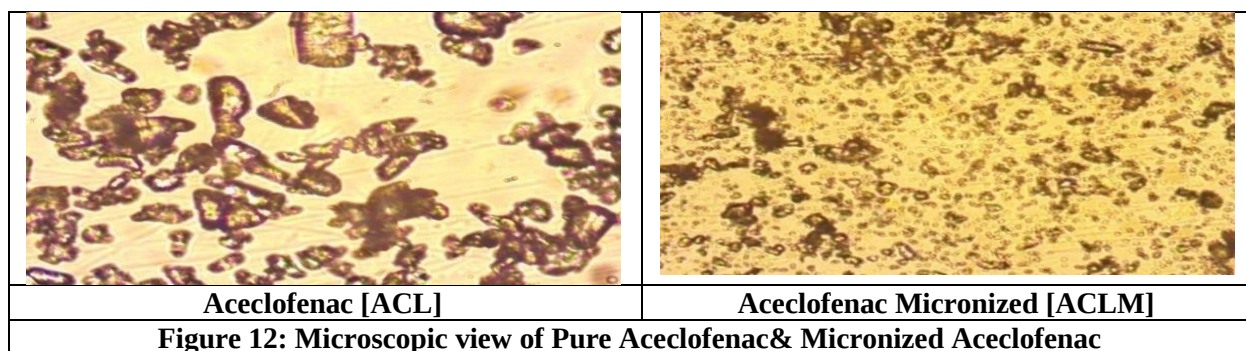


Figure 12: Microscopic view of Pure Aceclofenac& Micronized Aceclofenac

j) Scanning Electron Microscopy (SEM)

The SEM image of pure Aceclofenac and micronized Aceclofenac are represented in figure13. The $10,000\times$ magnification were selected to study surface morphology of the powders.

Pure Aceclofenac shows elongated hexagons type crystalline structure whereas micronized Aceclofenac appeared as fine irregular shape particles with smooth surfaces partially agglomerated in bundles. Hence, the morphology of Aceclofenac is improved after Micronization and crystals become much smaller than pure drug.

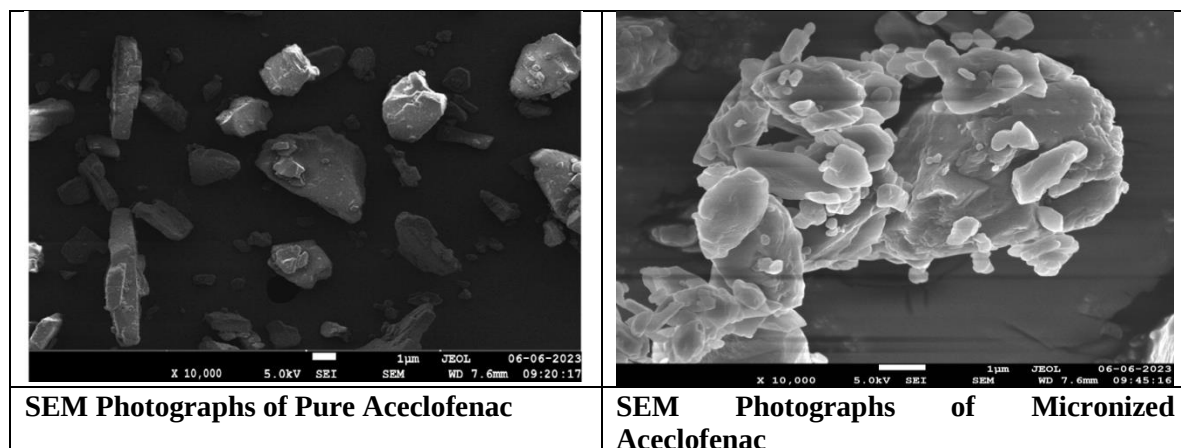


Figure 13: SEM images of Pure Aceclofenac and Micronized Aceclofenac

CONCLUSIONS

Micronization technique improves the solubility of Aceclofenac by reducing their particle size and increasing their specific surface area and ultimately improve therapeutic performance (i.e. high aqueous solubility and indirectly linked to improve permeability & ultimately increase bioavailability). Hence, Micronization techniques not only improve aqueous solubility but also ultimately reduce the cost of formulation.

REFERENCES

1. Chien YW, Lin S. Encyclopedia of Pharmaceutical Technology. Edn3, Vol. 1, Marcel Dekker, Inc. New York, 2007, 1082-1103.
2. Banakar UV. Pharmaceutical Dissolution Testing. Vol. 49, Marcel Dekker, Inc. New York, 2005, 19-51.
3. Matthew NB, Sharon VM, Gossett AC. A high throughput approach of selecting excipients for solubility enhancement of BCS Class II active pharmaceutical ingredients for oral dosage forms. Chemical Engineering Research and Design. 2023;193: 751-758.
4. Iyer R, JovanovskaVP, Berginc K, Jaklic, Fabiani F, Harlacher C, Huzjak T, Sanchez-Felix MV. Amorphous Solid Dispersions (ASDs): The Influence of Material Properties, Manufacturing Processes and Analytical Technologies in Drug Product Development. Pharmaceutics. 2021; 13: 1682.
5. M9 Biopharmaceutics Classification System Based Biowaivers Guidance for Industry, ICH. May 2021 <https://www.fda.gov/media/148472/download>.
6. Blokhina S, Sharapova A, Ol'khovich M, Perlovich G. Thermodynamic study of aceclofenac solubility, distribution and sublimation. The Journal of Chemical Thermodynamics. 2019; 137:13-21.
7. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility Enhancement Technique: A Review. Journal of Pharmaceutical Sciences and Research. 2018; 10(9): 2205-2211.
8. Loha ZH, Samanta AK, Heng PW. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian Journal of Pharmaceutical Sciences. 2015;10(4): 255-274.
9. Hickey AJ, Ganderton D. Pharmaceutical process engineering. Marcel Dekker Inc. New York, 2001, 174-197.
10. Saleem IY, Smyth HDC. Micronization of a soft material: airjet and micro-ball milling. AAPS PharmSciTech. 2010; 11: 1642-1649.
11. Shariare MH, Blagden N, Matas MD, Leusen FJJ, York P. Influence of solvent on the morphology and subsequent comminution of ibuprofen crystals by air jet milling. Journal of Pharmaceutical Sciences. 2012; 101: 1108-1119.
12. Brodka-Pfeiffer K, Hausler HP, Grass P. Air jet milling with homogeneous premixes of fenoterol hydrobromide and glucose for the application in dry powder inhalers. Die Pharmazeutische Industrie. 2005; 67(6):713-719.
13. Jain RA, Brito L, Straub JA, Tessier T, Bernstein H. Effect of powder processing on performance of fenofibrate formulations. European Journal of Pharmaceutics and Biopharmaceutics. 2008; 69: 727-734.
14. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian Journal of Pharmaceutical Sciences. 2014; 9: 304-316.
15. Midoux N, Hosek P, Pailleres L, Authelin J. Micronization of pharmaceutical substances in a spiral jet mill. Powder Technology. 1999; 104: 113-120.
16. Berry CE. Modern machines for dry size reduction in fine size range. Industrial and Engineering Chemistry. 1946; 38 (7): 672-678.
17. Midoux P, Hosek L, Pailleres L, Authelin JR. Micronization of pharmaceutical substances in a spiral jet mill. Powder Technology. 1999; 104: 113-120.
18. Brosh T, Kalman H, Levy A, Peyron I, Ricard F. DEM-CFD simulation of particle comminution in jet-mill. Powder Technology. 2014; 257: 104-112.
19. Kozawa K, Takafumi S, Yoshio O. Development of a spiral-flow jet mill with improved classification performance. Advanced Powder Technology. 2012; 23: 601-606.
20. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohel MC, Gandhi TR. Improvement of dissolution rate of Aceclofenac by solid dispersion technique. Powder Technology. 2011; 207: 47-54.
21. Napur MA, Rahman MM, Akter K, Hanif KB, Sharna JF, Sarker MS, Wahed MII. Preparation and characterization of naproxen solid dispersion using different hydrophilic carriers and in-vivo evaluation of its analgesic activity in mice. Heliyon. 2023; 9: e15432.

22. Alshehri S, Imam SS, Altamimi MA, Hussain A, Shakeel F, Elzayat E, Mohsin K, Ibrahim M, Alanazi F. Enhanced dissolution of Luteolin by solid dispersion prepared by different Methods: Physicochemical characterization and antioxidant activity. *ACS Omega*. 2020; 5:6461-6471.
23. Srivastava A, Khan MA, Bedi S, Bhandari U. Design, optimization and characterization of a novel amorphous solid dispersion formulation for enhancement of solubility and dissolution of Ticagrelor. *International Journal of Applied Pharmaceutics*. 2023; 15(4): 296-305.
24. United States Pharmacopeia and National Formulary (USP 41-NF 36). United States Pharmacopeial Convention <616> Bulk Density and Tapped Density of Powders. 2016. Accessed January 15, 2023.
25. United States Pharmacopeia and National Formulary (USP 41-NF 36). United States Pharmacopeial Convention <1174> Powder Flow. 2016.
26. Indian Pharmacopoeia, 6th Ed. Government of India, The Controller of Publications, New Delhi, Vol. III, 2010; 2213.