RESEARCH ARTICLE

Solubility Enhancement of Poorly Water-Soluble Aceclofenac by Amalgamation Micronization and Solid Dispersion Techniques

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ABSTRACT

Aceclofenac is a poorly aqueous soluble Biopharmaceutical Classification System (BCS) class II drug that has bioavailability problems after oral administration due to low aqueous solubility. There are numerous solubility modification approaches and they also have process limitations. Hence, the present research work aims to use two different solubility enhancement techniques (Micronization with Solid dispersion) simultaneously to counter individual limitations of techniques. The micronization technique increases the solubility of pure aceclofenac through increasing particle surface area, but it produces charged micronized material, leading to segregation and clumping of micronized material. Hence, micronized material handling during dosage form manufacturing is quite difficult. In the present research work, aceclofenac material is micronized by air jet mill to produce materials of below 25 µm size ranges. This micronized aceclofenac material is further encapsulated in a solid dispersion technique to produce amorphous aceclofenac materials. Solid dispersion of micronized aceclofenac was prepared by various techniques like physical kneading, solvent evaporation, melting and a combination thereof using different polymers (Polyox 301, HPMC, cetostearyl alcohol and glyceryl behenate). The prepared solid dispersion formulation (SD-31, SD-22, SD-23 and SD-30) exhibited an increase in the dissolution of aceclofenac as compared to pure aceclofenac. Various characterization techniques (Differential scanning calorimetry (DSC), X-ray Diffraction (XRD) and scanning electron microscope (SEM)) also reveal that aceclofenac crystallinity is significantly minimized in Solid dispersion formulation of SD-31, SD-22, SD-23 and SD-30. This selected solid dispersion (SD-31 and SD-22) also exhibited good stability (Photostability and stability at 40°C/75% RH after 3 months).

Keywords: BCS class, Solubility enhancement, Micronization, Solid dispersion, Aceclofenac, Stability.

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Conflict of interest: None

INTRODUCTION

Aceclofenac is a non-steroidal anti-inflammatory (NSAID) Biopharmaceutical Classification System (BCS) class II drug with anti-inflammatory and analgesic properties. Less solubility of aceclofenac in water requires drug modification properties.[1,2] The main object of this novel work is to improve the aqueous solubility of aceclofenac API by an amalgamation of two solubility enhancement techniques: micronization and solid dispersions. The micronization technique enhances the solubility by producing fine or micronized materials that have enhanced surface area.[3-8] However, the individual micronization technique has its limitations, such as particle agglomeration and difficulty handling fine particles of poor flowability.[9-14] These poorly flowable micronized particles can be easily encapsulated by solid dispersion technique[15-17] and produce a highly aqueous soluble formulation containing less or an optimized quantity of polymer formulations. The solid dispersion technique is use to enhance the solubility of APIs. Where one or more APIs are dispersed in an insert carrier by fusion, solvent or a combination methods.[18-20]

MATERIALS AND METHODS

Materials

As a gift sample, aceclofenac samples were procured from M/s Saral Chemtech LLP, India, M/s Aarti Drugs, India and M/s Windalas Biotech Ltd, India. Polyethylene oxide (Polyox WSR 301) and HPMC (Methocel K 100 LV) were received from M/s ColorconPvt. Ltd, Goa India. Cetostearyl alcohol (Kolliwax CSA50) and glyceryl behenate (Compritol 888 ATO) were received from M/s BASF, Germany and M/s Gattefosse,

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France. All other ingredients, chemicals and solvents (Isopropyl alcohol and distilled water) were of analytical grade.

Methods

Particle size distribution characterization of pure aceclofenac

Aceclofenac was characterized to its particle size distribution using Instrument Malvern Mastersizer 2000 (M/s Malvern Panalytical Ltd, United Kingdom). A small amount of sample (~50 mg) is required for analysis and results can be recorded within 10 minutes for each sample.

Micronization technique (spiral air jet mill)

It is well established that the micronization technique provides micronized APIs with increased surface area to improve solubility. Air Jet Mill was used for the micronization of a pure aceclofenac (ACL), which micronizes aceclofenac (ACLM) from a micrometer to nanometer size range. The aceclofenac powder was slowly added in the milling chamber along with moisture-free air through a venture and fine powder are collected in collection assembly.[6,8]

Solid dispersion technique using micronized aceclofenac

Solid dispersion of micronized aceclofenac were prepared with different Polymers (Polyox WSR 301, HPMC, Kolliwax CSA 50 and Compritol 888ATO) in a drug: polymer ratio of 1:0.05, 1:0.1, 1:0.2 and 1:0.5 by physical kneading (PM), melt fusion or melting method (MM), solvent evaporation or solvent kneading (SK) and a combination (Solvent evaporation and melting) thereof. Table 1 represents prepared different method of solid dispersion in polymer ratio with their formulation code.

Characterization and evaluation of solid dispersions

The micronized aceclofenac and its solid dispersion were characterized for particle size distribution, %Yield, drug content, saturation solubility study, density study, compressibility index (CI%), Hausner ratio (HR), flow property study, solid-state characterization (by Differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), Scanning electron microscopy (SEM), *In-vitro* dissolution study and stability study (Photostability and accelerated stability).[18-24]

RESULT AND DISCUSSIONS

Particle Size Distribution of Aceclofenac and Micronized Aceclofenac

The Malvern Mastersizer 2000 confirms that all three supplies of aceclofenac had d(0.9) value around or more than 100 µm. Air Jet Mill's reduced particle size of aceclofenac in a range of d(0.9) value 16.69 to 22.03 µm, d(0.5) value in a range of 5.60 to 8.43 µm and d(0.1) value 2.41 to 2.79 µm (Table 2). A comparative graph of the particle side distribution of all three manufacturers is represented in Figure 1.

Selection of Polymer

Polyox, HPMC, glyceryl behenate and cetostaeryl alcohols were selected for the solubility enhancement as a result of a compatibility study and disappearance of sharp melting point peak of aceclofenac in a physical mixture of 1:1 drug; Polymer ratio. The overlay DSC spectra of API with these excipients are shown in Figure 2.

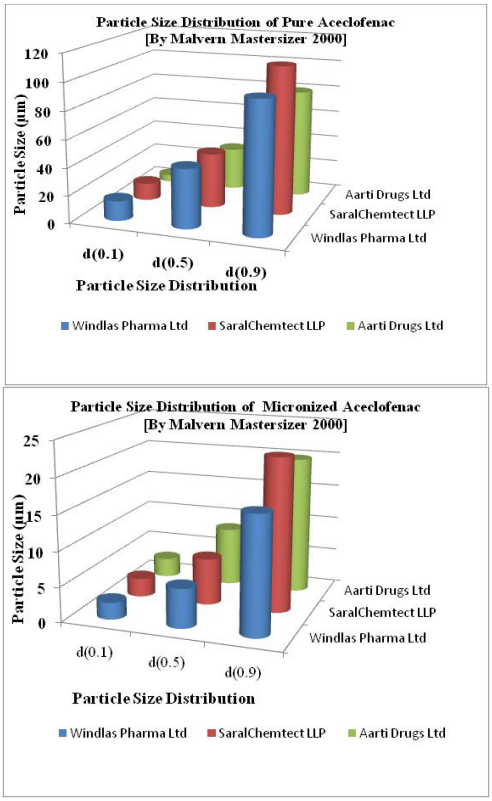


Figure 1: Particle size distribution of pure aceclofenac (ACL) and micronized aceclofenac (ACLM)

Characterization and Comparative Evaluation of Solid Dispersion of Micronized Aceclofenac

The %practical yield of micronized aceclofenac was 90.2% ± 0.77 and prepared solid dispersions were in a range of 96.25% ± 0.74 to 98.89% ± 0.48. The drug content of selected solid dispersions was found between 97.08% ± 0.1 to99.23% ± 0.1. The solid dispersion (combination of kneading and melting method) provides the highest drug content to be more than 97% with a low coefficient of variation (< 1.0). The % practical yield and %drug content of solid dispersion formulations is graphically represented in Figures 3 and 4, respectively.

Saturation solubility study results indicate that micronized aceclofenac increases aqueous solubility around 0.135 ± 0.02 mg/mL compared to pure aceclofenac solubility of 0.056 ± 0.01 mg/mL. The maximum solubility of around 0.43 ± 0.011 to 0.56 ± 0.01 mg/mL were found in polyox-based solid dispersion physical mixture (SD-3) or solid dispersion of all four polymers prepared by a combination of solvent kneading and melting method (SD-23 and SD-30). The coefficient of variation < 0.1%. The solubility study depicts that the solubility of aceclofenac increases with increasing drug-polymer ratio (1:0.05–1:0.5) prepared by a combination of solvent kneading and melting method (Figure 5).

Table 1: Formulation composition of solid dispersion

Sample code	*Drug*	*Polymer details*	*Preparation technique*	*Drug polymer ratio*
ACL	Pure aceclofenac	-	-	-
ACLM	Aceclofenac micronized	-	Air Jet milling	-
SD-1	ACLM	Polyox WSR301	Physical kneading (PM)	1:0.1
SD-2	ACLM	Polyox WSR301	Physical kneading (PM)	1:0.2
SD-3	ACLM	Polyox WSR301	Physical kneading (PM)	1:0.5
SD-4	ACLM	Polyox WSR301	Solvent Kneading (SK)	1:0.1
SD-5	ACLM	Polyox WSR301	Solvent Kneading (SK)	1:0.2
SD-6	ACLM	Polyox WSR301	Solvent Kneading (SK)	1:0.5
SD-7	ACLM	HPMC K 100 LV	Solvent Kneading (SK)	1:0.1
SD-8	ACLM	HPMC K 100 LV	Solvent Kneading (SK)	1:0.2
SD-9	ACLM	HPMC K 100 LV	Solvent Kneading (SK)	1:0.5
SD-10	ACLM	Polyox WSR301+HPMC K 100 LV	Solvent Kneading (SK)	1:0.1
SD-11	ACLM	Polyox WSR301+HPMC K 100 LV	Solvent Kneading (SK)	1:0.2
SD-12	ACLM	Compritol 888 ATO	Melting Method (MM)	1:0.1
SD-13	ACLM	Compritol 888 ATO	Melting Method (MM)	1:0.2
SD-14	ACLM	Compritol 888 ATO	Melting Method (MM)	1:0.5
SD-15	ACLM	Kolliwax CSA 50	Melting Method (MM)	1:0.1
SD-16	ACLM	Kolliwax CSA 50	Melting Method (MM)	1:0.2
SD-17	ACLM	Kolliwax CSA 50	Melting Method (MM)	1:0.5
SD-18	ACLM	Compritol 888 ATO + Kolliwax CSA 50	Physical kneading (PM)	1:0.1
SD-19	ACLM	Compritol 888 ATO + Kolliwax CSA 50	Physical kneading (PM)	1:0.2
SD-20	ACLM	Compritol 888 ATO + Kolliwax CSA 50	Melting Method (MM)	1:0.1
SD-21	ACLM	Compritol 888 ATO + Kolliwax CSA 50	Melting Method (MM)	1:0.2
SD-31	ACLM	Poyox+ HPMC+ Compritol+ Kolliwax	Solvent + Melting Method	1:0.05
SD-22	ACLM	Poyox+ HPMC+ Compritol+ Kolliwax	Solvent + Melting Method	1:0.1
SD-23	ACLM	Poyox+ HPMC+ Compritol+ Kolliwax	Solvent + Melting Method	1:0.1
SD-30	ACLM	Poyox+ HPMC+ Compritol+ Kolliwax	Solvent + Melting Method	1:0.5

Table 2: Particle size distribution of pure aceclofenac (ACL) and micronized aceclofenac (ACLM)

S. No.	*Manufacturer/Supplier*	*d(0.1) µm*	*d(0.5) µm*	*d(0.9) µm*	*Aceclofenac*
1	Windlas Biotech Ltd. [B.No. OCI/ACF/202209055]	14.444	43.161	95.285	Pure aceclofenac (ACL)
		2.417	5.602	16.686	Micronized aceclofenac (ACLM)
2	Saral Chemtech LLP [B.No. SCT/ACF/409/22-23]	12.651	40.273	108.054	Pure aceclofenac (ACL)
		2.679	6.695	22.033	Micronized aceclofenac (ACLM)
3	Aarti Drugs Ltd. [B. No. ACL/10070019]	5.000	31.000	80.000	Pure aceclofenac (ACL)
		2.791	8.434	19.85	Micronized aceclofenac (ACLM)

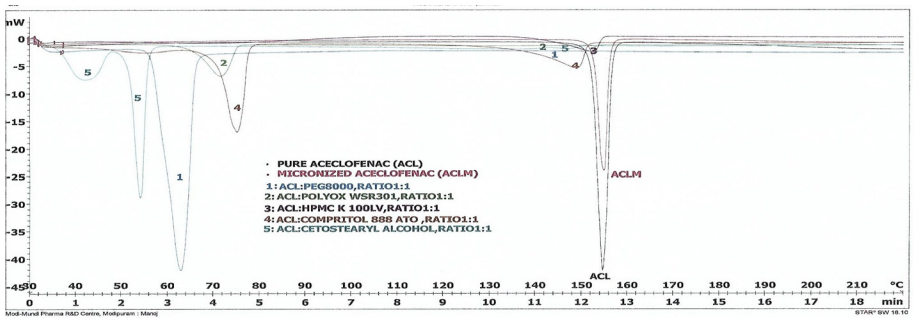


Figure 2: Overlay DSC spectra of pure aceclofenac, micronized aceclofenac and different physical mixture of excipients (1:1).

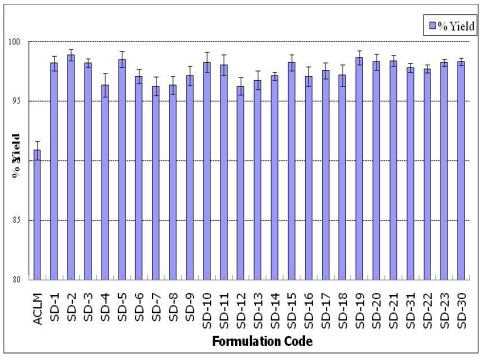


Figure 3: %Practical yield of solid dispersion

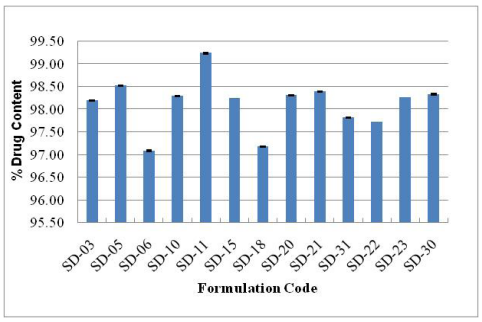


Figure 4: %Drug contents in solid dispersion

The physical characteristics of micronized aceclofenac and their solid dispersions are highlighted in Table 3.

Results indicate that micronized aceclofenac has very poor flow properties and is difficult to handle during the manufacturing of dosage form. Whereas prepared optimum selected solid dispersion (SD-31, SD-22, SD-23 and SD-30) shows angle of repose value from 31.31° ± 2.74 to 34.90 ± 1.42, indicating good flow property.

In-vitro Dissolution Study

The *in-vitro* dissolution profile (n = 6) of pure aceclofenac (ALC), micronized aceclofenac (ACLM) and selected batches of solid dispersion in 7.5 pH phosphate buffer are shown in Table 4 and in Figure 6. It is clearly observed that the rate of dissolution of pure aceclofenac is only 44.5% ± 6.0 in 60 minutes, whereas micronized aceclofenac shows 73.0% ± 1.4 and solid dispersion of combination of all four polymers (all four ratios) and a combination method shows more than 75% ± 1.5 within 60 minutes. It is also indicated that the combination method increases *in-vitro* drug dissolution more than 28% ± 1.8 drug in the first 10 minutes as compared to pure aceclofenac (only 3.2% ± 0.4) and micronized aceclofenac (19.5% ± 1.3).

Solid State Characterization of Solid dispersions

Differential scanning calorimetry

A sharp endothermic peak is observed in pure aceclofenac and micronized aceclofenac at 153.19 and at 153.57°C, respectively, analogs to its melting point during DSC analysis. In contrast, a peak corresponding to aceclofenac was absent in the DSC thermogram of SD-30 solid dispersions. Other ratios of the same composition (SD-31, SD-22 and SD-22) have very low

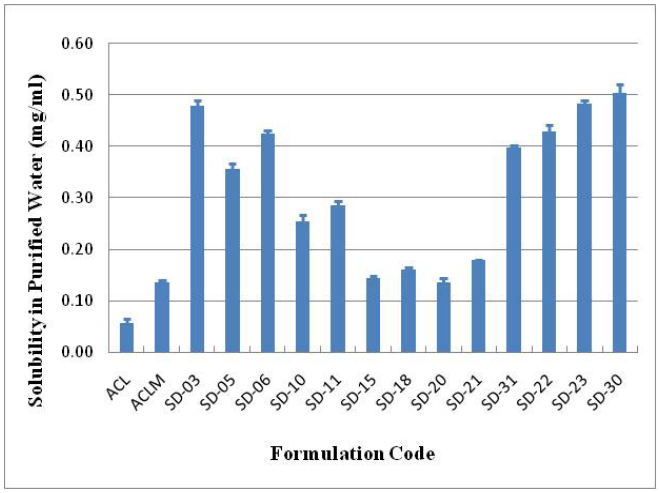


Figure 5: Solubility of Solid dispersion formulation in purified water

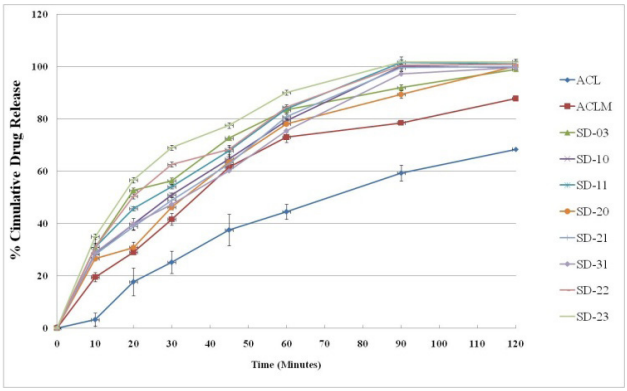


Figure 6: *In-vitro* dissolution of selected solid dispersions with respect to time

intensity peaks. As the polymer ratio increases from 1:0.05 to 1:0.5, the peak intensity is decreased and a complete disappearance of the peak is observed at 1:0.5 ratios (Figure 7). This suggests that a complete solution of aceclofenac has formed in said formulations and conversion of aceclofenac in amorphous form.

Fourier transform infrared spectroscopy

An overlay FTIR spectrum reveals that all major peaks of aceclofenac are visible. From the above observations, it has been concluded that there is no major shift in the peaks of aceclofenac (Figure 8). Hence, FTIR spectra reveal that there is NO incompatibility between the drug-polymer physical mixture and solid dispersion methods.

X-ray diffraction

The XRD spectra of pure aceclofenac and micronized aceclofenac illustrated strong and sharp peaks at a diffraction angle (2θ) of about 17, 22, 25 and 26° with intensity of more than 60 lakhs counts, suggesting that well-defined crystal structure of aceclofenac (Figure 9). There is a disappearance or weakness of the above strong and sharp peak when solid dispersions are prepared by combining all 4 polymers with solvent (SD-31, SD-22, SD-23 and SD-30) corresponding to

Table 3: Physical and flow characteristics of pure ACL, ACLM and solid dispersion formulations

Sample Code	*Bulk density (g/mL) Mean ± SD (n = 3)*	*Tapped density (g/mL) Mean ± SD (n = 3)*	*Compressibility index (CI) (%) Mean ± SD (n = 3)*	*Hausner ratio (HR) Mean ± SD (n = 3)*	*Angle of repose*	*Flow character*
ACL	0.313 ± 0.1	0.444 ± 0.1	29.69 ± 0.1	1.422 ± 0.2	46.23 ± 0.15	Poor
ACLM	0.122 ± 0.1	0.250 ± 0.1	51.22 ± 0.2	2.050 ± 0.6	64.68 ± 1.22	Very Poor
SD-3	0.319 ± 0.1	0.577 ± 0.1	44.68 ± 0.8	1.808 ± 0.3	58.80 ± 1.78	Very Poor
SD-5	0.203 ± 0.1	0.300 ± 0.1	32.43 ± 0.1	1.480 ± 0.5	58.33 ± 1.67	Very Poor
SD-6	0.208 ± 0.2	0.288 ± 0.2	27.78 ± 0.1	1.385 ± 0.4	47.36 ± 1.91	Poor
SD-10	0.208 ± 0.1	0.300 ± 0.1	30.56 ± 0.1	1.440 ± 0.1	46.62 ± 2.26	Poor
SD-11	0.214 ± 0.1	0.288 ± 0.1	25.71 ± 0.1	1.346 ± 0.1	46.78 ± 1.91	Poor
SD-15	0.385 ± 0.1	0.455 ± 0.1	15.38 ± 0.2	1.182 ± 0.7	34.97 ± 2.89	Good
SD-18	0.128 ± 0.1	0.200 ± 0.1	35.90 ± 0.4	1.560 ± 0.8	57.12 ± 2.38	Very Poor
SD-20	0.370 ± 0.1	0.455 ± 0.1	18.52 ± 0.2	1.227 ± 0.7	38.42 ± 0.42	Fair
SD-21	0.400 ± 0.1	0.476 ± 0.1	16.00 ± 0.1	1.190 ± 0.9	35.68 ± 0.62	Fair
SD-31	0.385 ± 0.1	0.444 ± 0.1	13.46 ± 0.1	1.156 ± 0.5	34.90 ± 1.42	Good
SD-22	0.385 ± 0.1	0.435 ± 0.1	11.54 ± 0.4	1.130 ± 0.1	34.55 ± 1.06	Good
SD-23	0.370 ± 0.1	0.417 ± 0.1	11.11 ± 0.3	1.125 ± 0.8	31.78 ± 0.97	Good
SD-30	0.370 ± 0.2	0.417 ± 0.2	11.11 ± 0.2	1.125 ± 0.1	31.31 ± 2.74	Good

Table 4: *In-vitro* dissolution data of selected solid dispersions

Sample Code	*%Drug release [Mean ± SD)] [n = 6]*						
Time (Minutes)	10	20	30	45	60	90	120
ACL	3.2 ± 0.4	17.7 ± 2.5	25.2 ± 5.3	37.5 ± 4.2	44.5 ± 6.0	59.3 ± 2.8	68.4 ± 3.1
ACLM	19.5 ± 1.3	29.0 ± 1.7	41.6 ± 0.9	61.6 ± 2.3	73.0 ± 1.4	78.5 ± 1.9	87.8 ± 0.6
SD-03	30.9 ± 3.7	52.7 ± 0.9	56.3 ± 1.2	72.6 ± 0.6	83.4 ± 1.2	92.0 ± 1.1	99.0 ± 0.8
SD-10	28.3 ± 1.1	39.8 ± 2.2	50.9 ± 0.9	64.7 ± 3.6	79.3 ± 0.9	100.2 ± 1.8	99.6 ± 1.4
SD-11	31.0 ± 1.5	46.0 ± 0.8	54.0 ± 0.8	68.0 ± 2.2	84.0 ± 1.1	102.0 ± 2.2	101.0 ± 1.0
SD-20	26.6 ± 0.7	30.8 ± 2.1	46.2 ± 1.0	63.4 ± 2.9	78.1 ± 0.6	89.4 ± 1.5	100.1 ± 1.1
SD-21	28.1 ± 1.6	38.8 ± 1.4	48.9 ± 1.2	62.7 ± 1.2	80.9 ± 1.0	99.6 ± 1.4	100.0 ± 0.5
SD-31	28.9 ± 1.2	39.8 ± 2.4	47.2 ± 1.1	60.2 ± 4.1	75.4 ± 1.3	97.2 ± 1.8	99.6 ± 1.4
SD-22	31.0 ± 1.3	50.4 ± 0.8	62.6 ± 1.4	68.3 ± 2.0	84.5 ± 0.4	100.5 ± 1.4	100.8 ± 0.9
SD-23	35.0 ± 1.8	56.6 ± 1.2	69.0 ± 1.6	77.5 ± 1.5	90.1 ± 1.2	101.7 ± 0.8	101.8 ± 1.5

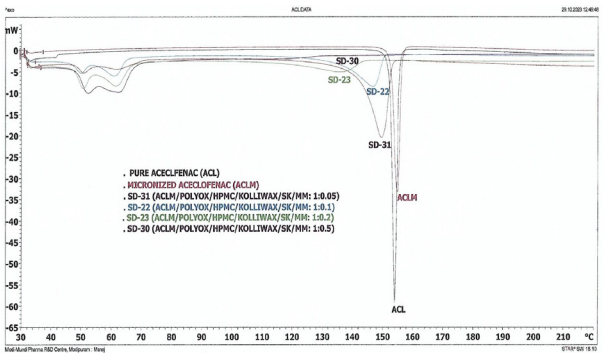


Figure 7: A DSC thermogram of pure ACL, ACLM and selected optimum solid dispersion formulations

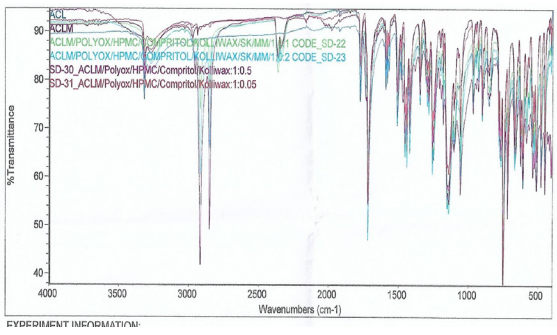
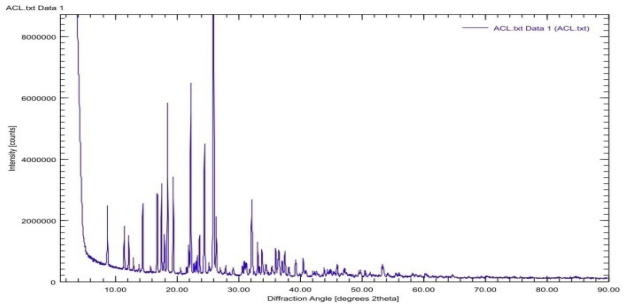
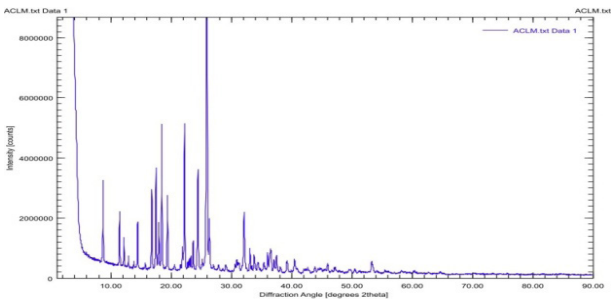


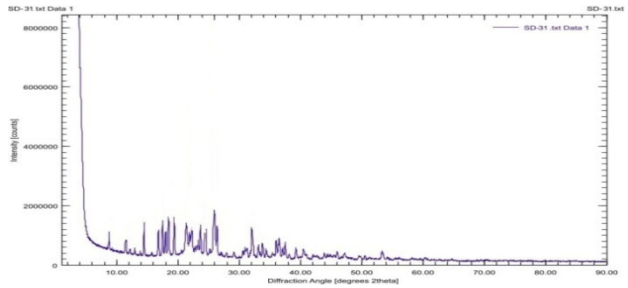
Figure 8: Characteristics FTIR Spectra peaks data of pure ACL, ACLM and selected optimum solid dispersion formulations



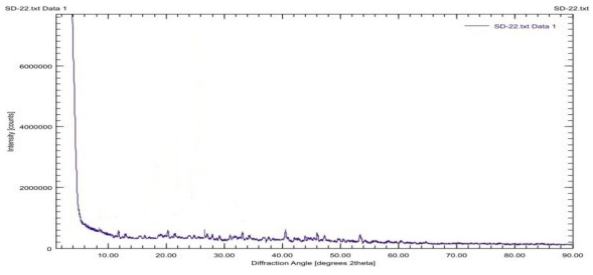
Pure ACL



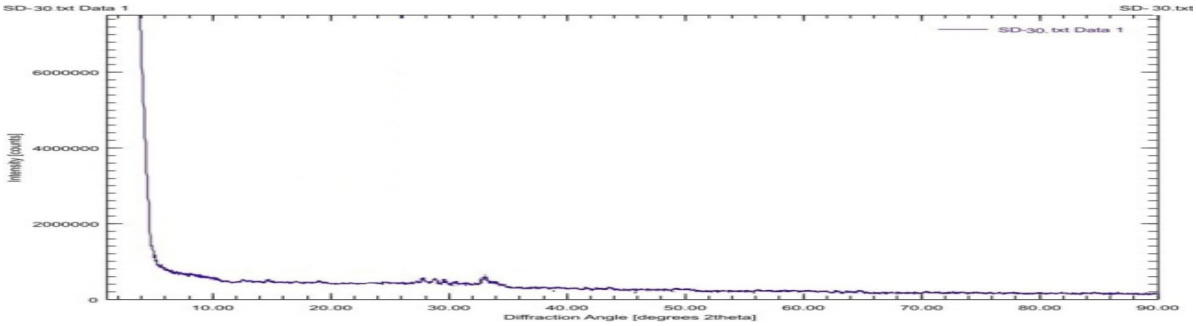
ACLM



Solid dispersion formulation; SD-31



Solid dispersion formulation; SD-22



Solid dispersion formulation; SD-30

Figure 9: XRD spectra of aceclofenac, micronized aceclofenac and solid dispersion formulations

pure aceclofenac peaks. Hence, it is confirmed that the solid dispersion formulation changes aceclofenac's crystallinity into an amorphous form.

Scanning electron microscopy

The SEM image of aceclofenac shows elongated hexagons type crystalline structure, whereas micronized aceclofenac appeared as fine irregular shape particles with smooth surfaces partially agglomerated in bundles (Figure 10). Hence, the morphology of aceclofenac is improved after micronization, and crystals become much smaller than those of pure drugs. The modified drug particle shape of aceclofenac solid dispersion appears in SEM and suggests reduced crystalline nature of aceclofenac material.

Stability Study and Photostability Study

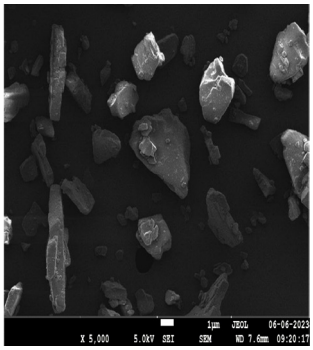
Stability study

The solid dispersions formulations SD-31 and SD-22 show satisfactory assay content of 97.22 and 98.01%, respectively at 40°C/75% RH after 3 months of storage. The related substance level were according to the specification limits (Total impurity NMT0.7). Hence, both of the formulations can be considered stable. Figures 11 and 12 show stability study results.

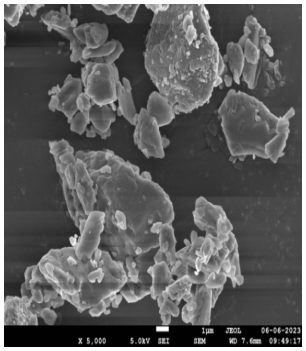
Photostability study

The photostability study of optimized solid dispersion (SD-31 and SD-22) was also found satisfactory when the sample was exposed in a photostability chamber for 6 days in clear glass bottles (as per ICH Guideline Q1B 'Photo stability study of new drug substance and Products'). Photostability study results indicated no significant change in assay content and related substances (Figures 13 and 14).

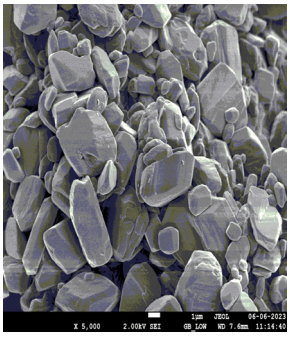
All the results are within the specifications. Therefore, based on the results, clear glass bottles are suitable for sufficiently protecting the final solid dispersion formulation from light exposure. The photostability study was conducted successfully, and it concluded that solid dispersion formulation is stable against UV-vis light, per the ICH guidelines.



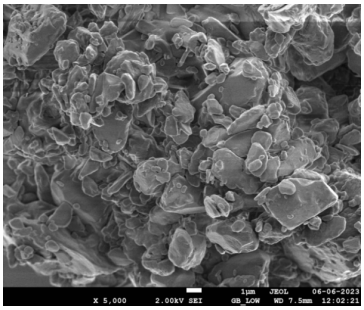
Pure aceclofenac



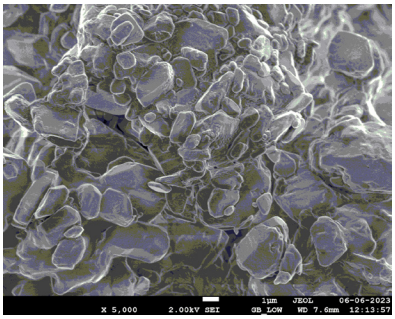
Micronized aceclofenac



Solid dispersion (SD-31)

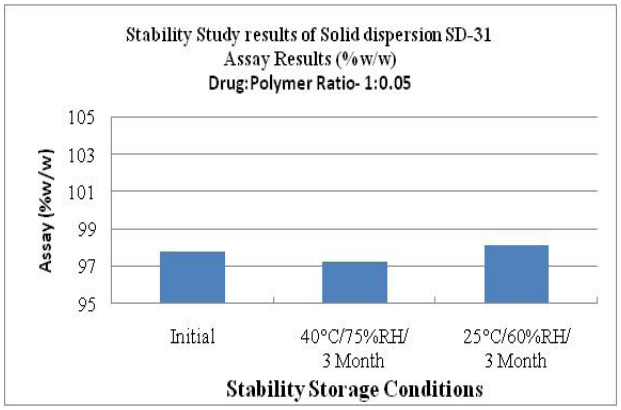


Solid dispersion (SD-22)



Solid dispersion (SD-23)

Figure 10: SEM images of pure aceclofenac, micronized aceclofenac and solid dispersion formulations



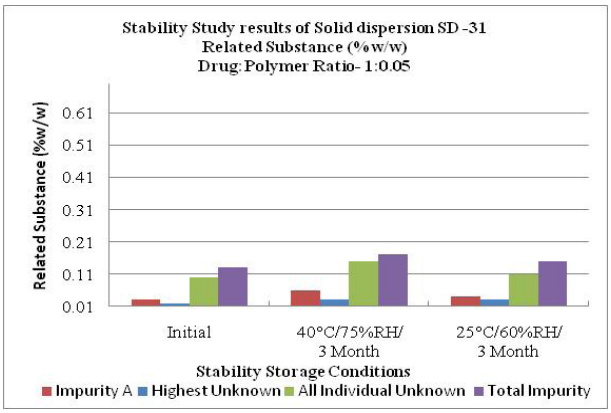
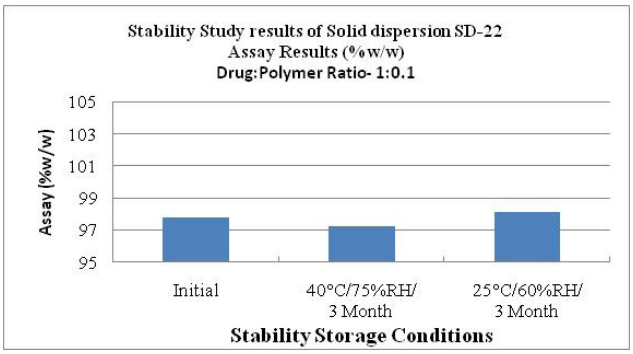


Figure 11: Stability study results of solid dispersion formulation; SD-31



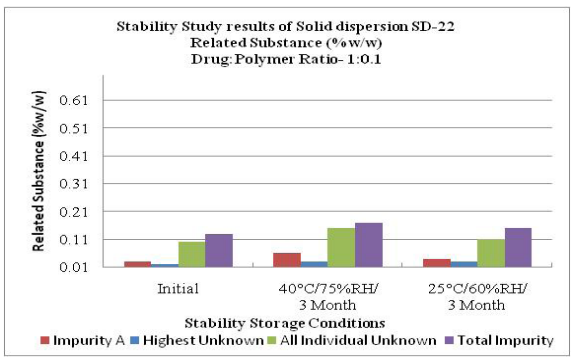


Figure 12: Stability study results of solid dispersion formulation; SD-22

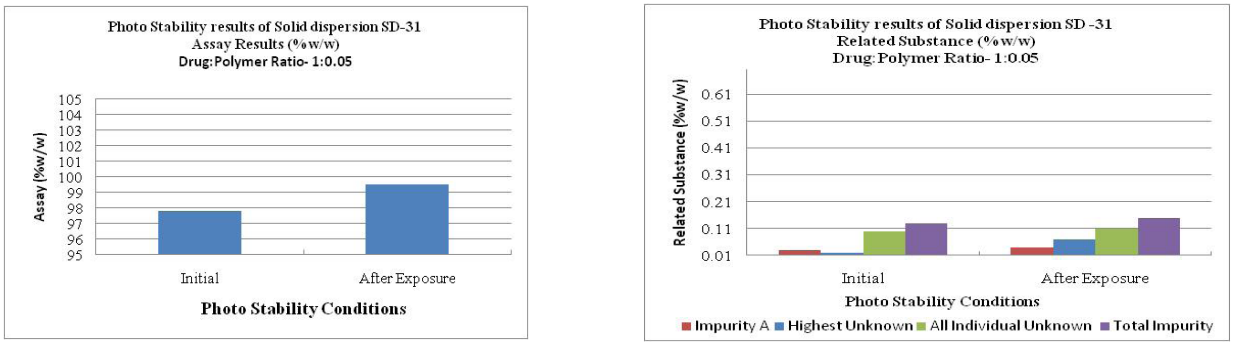


Figure 13: Photo Stability study results of solid dispersion formulation; SD-31

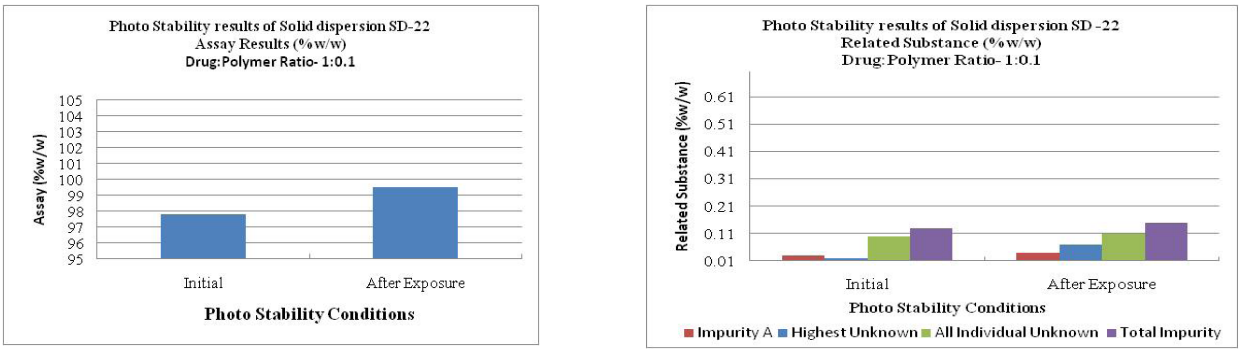


Figure 14: Photo Stability study results of solid dispersion formulation; SD-22

CONCLUSION

In this research work, an amalgamation of both solubility enhancement techniques (Micronization and Solid dispersion) provides not only proper handling of micronized material but also provides a satisfactory dosage from the manufacturing process for aceclofenac API (very low concentration of drug: polymer ratio, reproducibility, high aqueous solubility formulation, increased bioavailability, high content uniformity and dosage form stability). Micronization and dispersion in the combination of two or more polymers with two or more manufacturing methods make pharmaceutical manufacturing methods suitable. These techniques ultimately reduce the cost of formulation with enhanced aqueous solubility of poorly soluble drugs.

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