UNICORN
REDIFINING RESEARCH

Journal of
CURRENT PHARMA
Research
www.jcpronline.in/

Journal of Current Pharma Research 6 (1), 2015, 1740-1750.

Research Article

Effect of Polyethylene Glycol on Physiochemical Properties of Spherical Agglomerates of Aceclofenac.

S. V. Patil*, S. S. Pail
Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadagoan, Maharashtra, India.

Received 11 Dec. 2015; received in revised form 21 Dec. 2015; accepted 22 Dec. 2015
Available online 27 December 2015.

Abstract
Spherically agglomerated crystals of Aceclofenac (ACF) of improved flowability, compactibility, solubility and dissolution with good stability were successfully prepared by emulsion solvent diffusion method. Plane agglomerates and agglomerates with polyethylene glycol 6000 (PEG) were prepared using methanol, chloroform and water as good solvent, bridging liquid and poor solvent respectively. Particle size, flowability and compactibility of plane and PEG agglomerates were preferably improved for direct tabletting compared with raw crystals of ACF. These improved properties of spherically agglomerated crystals were due to their large and spherical shape and enhanced fragmentation during compaction which was well supported by less elastic recovery of its compact. For agglomerates with PEG, solubility and rate of dissolution was improved than plane agglomerates. X-ray powder diffraction, differential scanning calorimetry and fourier transforms infrared spectroscopy study were indicated no any polymorphic transition of ACF.
Keywords: spherical crystallization, Aceclofenac, compactibility, packability.

1. Introduction
Tablet is the most preferred dosage form than any others as it is most stable, readily portable and consumed dosage form. Direct tabletting has been renewed an efficient process by mixing and compressing a powder to save time and cost as compared with granule tabletting.[1] But it strongly depends on the flowability, compactibility and packability of the drug crystals used otherwise lot of excipients are necessary resulting in bigger sized tablets. Crystal could be generated employing any of the available technique like sublimation, solvent evaporation, vapor diffusion, thermal treatment, crystallization from melt precipitation and growth in presence of additives.[2]

Corresponding author
E-mail address: sachinpatil79@rediffmail.com
(S.V. Patil)

Fine crystals are preferred over large crystals of poorly soluble pharmaceuticals as they provide greater bioavailability. However, micronization of crystals frequently prevents efficient powder processing due to poor flowability, compactibility and packability.[3] Thus novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during recrystallization process has been desired. The use of spherical crystallization technique appears to be efficient alternative for obtaining suitable particles for direct compression.[4] Spherical crystallization is a particle design technique by which recrystallization and agglomeration can be carried out simultaneously in one step which has been successfully utilized for improvement of flowability and compactibility of crystalline drugs. [5, 6, 7] Two methods are reported in the literature for generating spherical agglomerates: the spherical agglomeration (SA) method and emulsion solvent diffusion (ESD) method.[8, 9] In SA method nearly saturated solution of the drug in the good solvent is poured into the poor solvent, provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and good solvent. Under agitation a third solvent called bridging liquid is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals.[10] In ESD method the drug is dissolved in the good solvent and bridging liquid and the resultant solution is dispersed into the poor solvent producing emulsion (quasi) droplets, even though the pure solvents are miscible. In this method the affinity between the drug and good solvent is stronger than that of good solvent and poor solvent. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase and the poor solvent diffuses into the droplets by which drug crystallizes inside the droplets.[11]

Aceclofenac (ACF) is NSAID drug having poor compressibility.[12] In present study spherical agglomerates of ACF were prepared by ESD method to improve physicochemical properties. The aim of present investigation was to study the effect of addition of PEG during spherical agglomeration of ACF on physicochemical properties.

Materials and Methods

Materials

Aceclofenac (ACF) was kindly provided by Alembic research Centre, Gujarat, India. Polyethylene glycol 6000 (PEG), methanol and chloroform were purchased from Rajesh chemicals, Pune, India.

Methods

Development of spherically agglomerated crystals of ACF by ESD method

ACF (1g) was dissolved in a mixture of 6ml methanol (good solvent) and 4ml chloroform (bridging liquid). The resultant solution was poured in to distilled water (50ml) containing 500mg / 1gm of PEG, with stirring at 800 revolutions per minute (rpm) for 20 minutes at 25°C. The obtained recrystallized agglomerates were collected by vacuum filtration and dried in oven at 60° C for 4 hours (hrs). The dried crystals were stored in desiccators at room temperature before use. Above process was repeated several times to obtain enough materials for characterization and to observe reproducibility.

Micrometric properties of raw crystals and spherical agglomerates

Mean particle size of ACF and its agglomerates was determined by randomly counting average diameter of 100 particles with optical microscope and their SEM microphotographs were taken. Micrometric properties of raw crystals and spherical agglomerates were determined. Particle size was determined by microscopy method. Bulk density and tap density was determined according to following method. A 50 ml glass cylinder was weighed and filled with 30 ml sample and reweighed. The opening was secured with parafilm. The cylinder was gently reversed once and the powder was carefully leveled without compacting. Bulk volume was determined after one mechanical tap on a tap density tester (Dolphin™). Tap volume was measured after 2000 taps.[13] Each analysis was repeated thrice. Values of bulk density and tap density were used to calculate Carr's index and Hausners ratio in equation 1 and 2 respectively.[14, 15]

Carr's index= [(Tap density- Bulk density)/Tap density] X 100 (1)

Hausners ratio=

Tap density/Bulk density (2)

The flow behavior of raw crystals and spherical agglomerates was determined by Angle of repose using fixed funnel method.[16]

Compaction behavior of raw crystals and spherical agglomerates

Compaction behavior of raw crystals and spherical agglomerates were analyzed by Heckel equation, elastic recovery (ER) and crushing strength. The Heckel method was most frequently. It is assumed that the densification of the powdered column follows a first order kinetics. Thus the degree of material densification is correlated to its porosity. [17, 18] The Heckel equation is widely used to evaluate the volume reduction of the materials when pressure is applied during compression and is as given below.

$$ln\ (1/1\text{-}D) = KP + A \qquad (3)$$

Where D is the relative density of powder for applied pressure P. The slope of the straight-line portion, K, is the reciprocal of the mean yield pressure (MYP), of the material. From the value of the intercept, A, the relative density, D_a and the relative density of powder bed at the point when the applied pressure equals to zero, D_o, can be calculated using following equations.

$$D_a = 1- e^{-A} \qquad (4)$$

$$D_o= 1- e^{-Ao} \qquad (5)$$

$$D_b = D_a - D_o \qquad (6)$$

Where A_o represents the intercept of the line when P = 0. The relative density, D_b, describes the phase of rearrangement at low pressure and is the difference between D_a and D_o.

Heckel study was performed by compressing 500 mg of raw crystals and spherical agglomerates on hydraulic press (Samrudhi Enterprises, Mumbai, India.) using 13 mm flat faced punch and die set, at pressure 20, 30, 40, 60, 80, 100 and 120 kN and thickness, weight and diameter of compacts were determined. M.Y.P., D_a, D_o and D_b were determined as per equation 3, 4, 5 and 6 respectively. For determination of ER thickness of the compact of agglomerates and raw crystal of ACF was determined at compression pressure 60 kN (H_c) and at 24 hrs after releasing the tablet (H_e). ER was calculated in equation 7.[19]

$$ER= [(H_e – H_c) /H_c] \times 100 \qquad (7)$$

Solubility study:

Solubility of raw crystals and spherical agglomerates of ACF were determined in distilled water. A 20 ml saturated solution of raw crystals and spherical agglomerates of ACF were prepared in distilled water by continuously shaking (300 rpm) at 25 ± 0.5°C for 48 hrs. Samples were filtered through 0.45 µm filter and assayed spectrophotometrically for drug content at 275 nm.

X-ray powder diffraction (XRPD)

X-ray powder diffraction of raw crystals and spherical agglomerates were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α– radiations (1.542 A°) and analyzed between 2-60° (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5 x 10^3 cycles/s and the chart speed was kept at 100 mm/2θ.

Differential Scanning calorimetry (DSC)

Thermal properties of raw crystals and spherical agglomerates of ACF were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 300°C at a heating rate of 10°C/ min.

Fourier transforms Infrared spectroscopy (FT-IR)

Fourier transforms Infrared spectroscopy of raw crystals and spherical agglomerates of ACF was recorded using Jasco V5300 (Jasco, Japan) FT-IR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm^{-1}.

In-Vitro dissolution studies

The dissolution studies were performed by using USP 26 type II dissolution test apparatus (Dolphin™, Mumbai, India). Dissolution medium used were pH 7.5 phosphate buffer 900 ml, temperature was maintained at 37 ± 2°C and 100 rpm stirring was provided for each dissolution study. ACF and its spherical agglomerates equivalent to 100 mg of ACF were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (pore size 25 µm), concentration of ACF was determined spectrophotometrically at 269 nm.

Stability studies

All spherical agglomerates of ACF were charged for the accelerated stability studies as per ICH guidelines (40 ± 2 °C C and75 ± 5% RH) for a period of 6 months in a stability chamber (Thermolab, Mumbai, India). The samples were placed in vials with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 30, 60, 90 and

180 days and evaluated for the drug content and *in vitro* drug release for 30 min.

Statistical analysis

Results are expressed as mean ± S.D for triplicate samples. The results were statistically analyzed and significant differences among formulation parameters were determined by one-way analysis of variance using 'Graph Pad Instate®' Version 3.05 (USA), statistical analysis program. Statistical significant was considered at $p < 0.05$.

Results and Discussion

Development of spherically agglomerated crystals of ACF by ESD method

A study started with selection of good solvent, poor solvent and bridging liquid which strongly depends on the miscibility of the solvents and the solubility drug in individual solvents. ACF is soluble in methanol, slightly soluble in chloroform but insoluble in water.[20] Thus methanol, chloroform and water were used as good solvent, bridging liquid and poor solvent respectively. Preliminary experiments were performed to optimize the concentration of solvents. It was found that without bridging liquid needle shaped agglomerates were formed. At optimized concentration of good solvent and bridging liquid (3:2) spherical agglomerates of ACF were formed. After optimizing concentration of solvents different stirring rates were tested and an optimum was found to be 800 rpm. Lower stirring rate reduced the possibility of formation of spherical agglomerates while high stirring rate destroyed the agglomerates. When solution of drug in good solvent and bridging liquid was poured into poor solvent the quasi-emulsion droplets of drug solution were produced initially. Successively the crystallization of a drug occurred at the outer surface of the droplet. The spherically agglomerated crystals were produced simultaneously after complete crystallization and the whole process is called as emulsion solvent diffusion. Under stirring the agglomerates were spheronized and compacted.

Micrometric properties of raw crystals and spherical agglomerates

Agglomerates formed were spherical having micrometric properties given in table 1. It was found that particle size of plane agglomerates and agglomerates with PEG (1% and 2%) was increased more than 10 times than original crystals may be due to particle agglomeration in the treated crystals. Microphotographs of drug, plane agglomerates and agglomerates with PEG (1% and 2%) shown in figure 1 and 2 revealed that agglomerates were spherical with smooth surface. The bulk density of plane agglomerates and agglomerates with PEG (1% and 2%) was lower than that of raw crystals of ACF. Reduction in bulk densities of spherical agglomerates indicates the greater porosity within the agglomerates.[21] Angle of repose, Carr's index and Hausners ratio values of the plane agglomerates and agglomerates with PEG (1% and 2%) was lower than raw crystals of ACF, indicates its better flowability might be due to large and spherical shape of agglomerates clearly indicated in microphotographs of agglomerates shown in figure 1. In case of agglomerates with PEG (1% and 2%) average diameter was increased than raw crystals but decreased than plane agglomerates of ACF. These findings suggests that PEG were poorly adsorbed at the surface which reduces the interfacial tension between bridging liquid and crystals and decreases the adhesive force acting to agglomerate the crystals.[22]

Compaction behavior of raw crystals and spherical agglomerates

The compressibility of a material is its ability to reduce in volume as a result of an applied pressure. Heckle parameters D_a, D_o, D_b, MYP and elastic recovery of raw crystals and spherical agglomerates of ACF were given in table 2. D_b value represents the particle rearrangement phase in early compression stage and tends to indicate extent of particle fragmentation. The D_b values for plane agglomerates and agglomerates with PEG (1% and 2%) were higher than the raw crystals of ACF indicated that the agglomerates were highly fractured during early stage of compression although fragmentation is followed by plastic deformation. The results were well supported by higher MYP values. The elastic recoveries of the compacts of plane agglomerates and agglomerates with PEG were smaller than that of original drug crystals. These findings suggested that the agglomerated crystals were easily fractured, and the new surface of crystals produced might contribute to promote.

Plastic deformation under compression. The improved compactibility of agglomerates might be attributed to characteristic structure responsible for the large relative volume changes during the early stage of the compression process due to their fragmentation. It has been shown that a reduction in bulk density of agglomerates results in an increase in the tensile strength of tablets, similar results were obtained in study by Nokhodchi A. and coworkers.[21]

Solubility study

Solubility of raw crystals and spherical agglomerates of ACF were given in table 3. It was observed that solubility of spherical agglomerates was increased than raw crystals of ACF may be due to increased in wettability and porosity. It was higher for agglomerates with 2% PEG and lower for plane agglomerates.

XRD, DSC and FTIR study

XRD, DSC and FTIR spectra of drug and agglomerates with 3% PEG shown in figure 2, 3 and 4 respectively were identical. It has indicated that no any polymorphic transition has occurred during crystallization ACF which reveals stable nature of drug during agglomeration process. The reduction in intensity (in XRD) and decrease in enthalpy in DSC) of the agglomerate has indicated modest amorphization of drug in the agglomerates.

In-Vitro dissolution studies

Rate of dissolution of raw crystals and spherical agglomerates of ACF were shown in figure 5. It was observed that for raw crystals of ACF up to 67 % drug was release in 30 min while for agglomerates of ACF drug release was increased with the order 2% PEG > 1%PEG > plane > raw crystals. The results were well correlated with solubility data.

Stability studies

The agglomerates did not show any significant change in drug content and *in vitro* drug release during stability study as given in table 5. It has indicated that the prepared agglomerates were adequately stable as per regulatory requirements.

Conclusion

Spherical crystals of ACF were successfully prepared by emulsion solvent diffusion method. Flowability, compactibility and packability were dramatically improved for plane agglomerates and agglomerates with 1% and 2% PEG compared with raw crystals of ACF resulting in successful direct tabletting without capping. Also remarkable fragmentation, increased tensile strength of plane agglomerates and agglomerates with PEG indicates improved compactibility. Improved solubility and dissolution of plane and agglomerates with PEG than raw crystal of ACF has shown their improved wettability. During agglomeration polymeric transition has occurred but not associated with changes at molecular level. It concludes that spherical crystallization of ACF with polyethylene glycol is a satisfactory method to improve flowability, compactibility and packability for direct tabletting.

Acknowledgments

The authors are also thankful to Shivaji University, Kolhapur for providing minor research grant for this project. The authors are also thankful to Alembic research Centre, Gujarat, India, for providing free gift sample of Aceclofenac.

References

1. Lieberman H. A., Lachman L. and Schwartz J. B. Pharmaceutical Dosage Forms- Tablets; Marcel Dekker: New York. 1989; 1st edition, p 195–246.
2. Guillory J. K. Polymorphism in pharmaceutical solids; Marcel Dekker: New York. 1999; 1st edition, p 183–226.
3. Kawashima Y. Development of spherical crystallization technique and its application to pharmaceutical systems. Arch. Pharm. Res. 1984; 7(2): 145–151.
4. Kawashima Y., Furukawa K. and Takenaka H. The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. Powder Technol. 1981; 30: 211.

5. Paradkar AR., Pawar AP., Mahadik KR. and Kadam SS. Spherical crystallization: a novel particle design technique. Indian Drugs. 1994; 31(6): 229–233.

6. Patil SV. and Sahoo SK. Spherical Crystallization: A method to improve tabletability. Research J. Pharm. and Tech. 2009; 2(2): 234–237.

7. Yadav AV. and Yadav VB. Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique. Journal of Pharmacy Research. 2008; 1(2): 105–112.

8. Ribardiere A., Tchoreloff P., Couarraz G. and Puisieux F. Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system. Int. J. Pharm. 1996; 144(2): 195–207.

9. Kawashima Y., Okumura M. and Takenaka H. Spherical crystallization: Direct spherical agglomeration of salicylic acid crystals during crystallization. Science. 1982; 216: 1127–1128.

10. Kawashima Y., Okumura M. and Takenaka H. The effects of temperature on the spherical crystallization of salicylic acid. Powder Technol. 1984; 39: 41–47.

11. Sano A., Kuriki T., Kawashima Y., Takeuchi H., Hino T. and Niwa T. Particle design of tolbutamide by spherical crystallization technique. V. Improvement of dissolution and bioavailability of direct compressed tablets prepared using tolbutamide agglomerated crystals. Chem. Pharm. Bull. 1992; 40: 3030–3035.

12. Sweetman S. Martindale: The extra pharmacopoeia; Pharmaceutical Press: London. 2003; 17th edition, p 333.

13. Zang Y., Law Y. and Chakrabarti S. Physical properties and compact analysis of commonly used direct compression binders. AAPS Pharm. Sci. Tech. 2003; 4(4): Article 62.

14. Carr RL. Evaluating flow properties of solids. Chem. Engg. 1965; 72: 163–168.

15. Hausner HH. Friction conditions in a mass of metal powder. Int. J. Powder Mettall. 1967; 3:7–13.

16. Lachman L., Liberman H. A. and Konig J. L. Theory and Practice of Industrial Pharmacy; Philadelphia PA, Lea and Febiger: Philadelphia. 1986; 3rd edition, p 317.

17. Heckel RW. An analysis of powder compaction phenomenon. Trans. Metal. Sci. AIME. 1961; 221: 1001–1008.

18. Heckel RW. Density-pressure relationships in powder compaction. Trans. Metal. Sci. AIME. 1961; 221: 671–675.

19. Armstrong NA. and Hainess-Nutt RF. Elastic recovery and surface area changes in compacted powder system. Powder Technol. 1974; 9: 287–290.

20. Maryadele J. The Merck Index; Merck and Co.: New York. 2001; 13th edition, p 1335.

21. Nokhodchi A., Maghsoodi M., Hassan-Zadeh D. and Berzegar-Jalali M. Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients. Powder Technol. 2007; 175: 73–81.

22. Kawashima Y., Handa T., Takeuchi H., Okumura M., Katou H. and Nagata O. Crystal modification of phenytoin with polyethylene glycol for improving mechanical strength, dissolution rate and bioavailability by a spherical crystallization technique. Chem. Pharm. Bull. 1986; 34: 3376–3386.

23. Shlomit W., Serguei F. and Jean H. U. S. Patent 0043094 A1, 2007.

24. Rai AK. and Rai DK. Spectroscopic studies of some antidiabetic drugs. Spectrochimica Acta Part A. 2003; 59: 1673–1680.

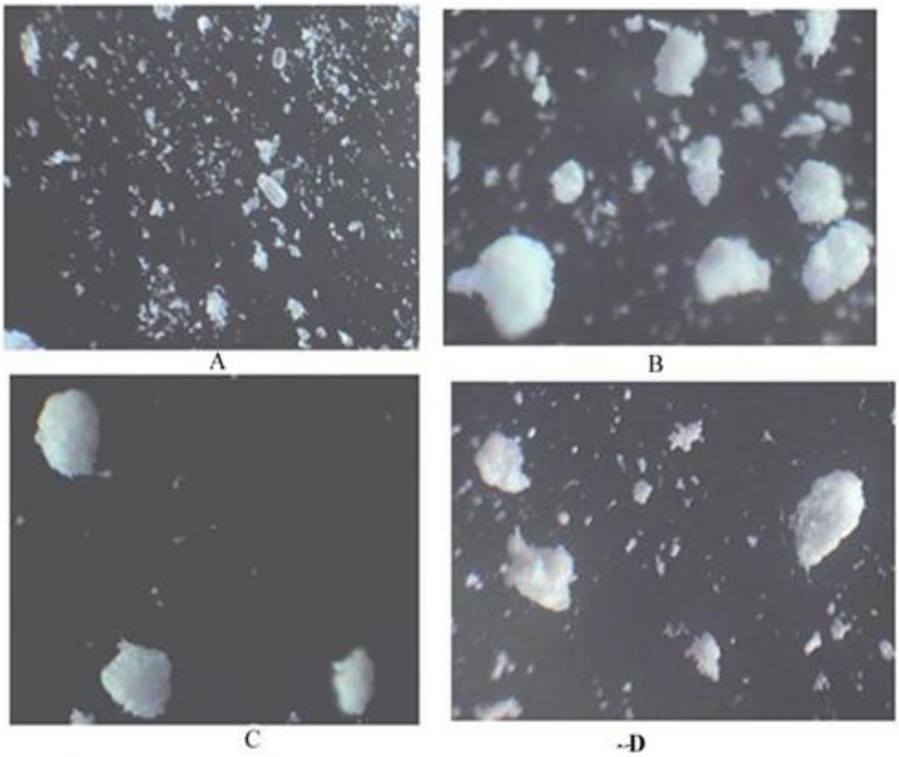

Figure 1: Microphotographs of A: Aceclofenac and Spherical agglomerates of ACF: B: Plane, C: with 1% PEG, D: with 2% PEG.

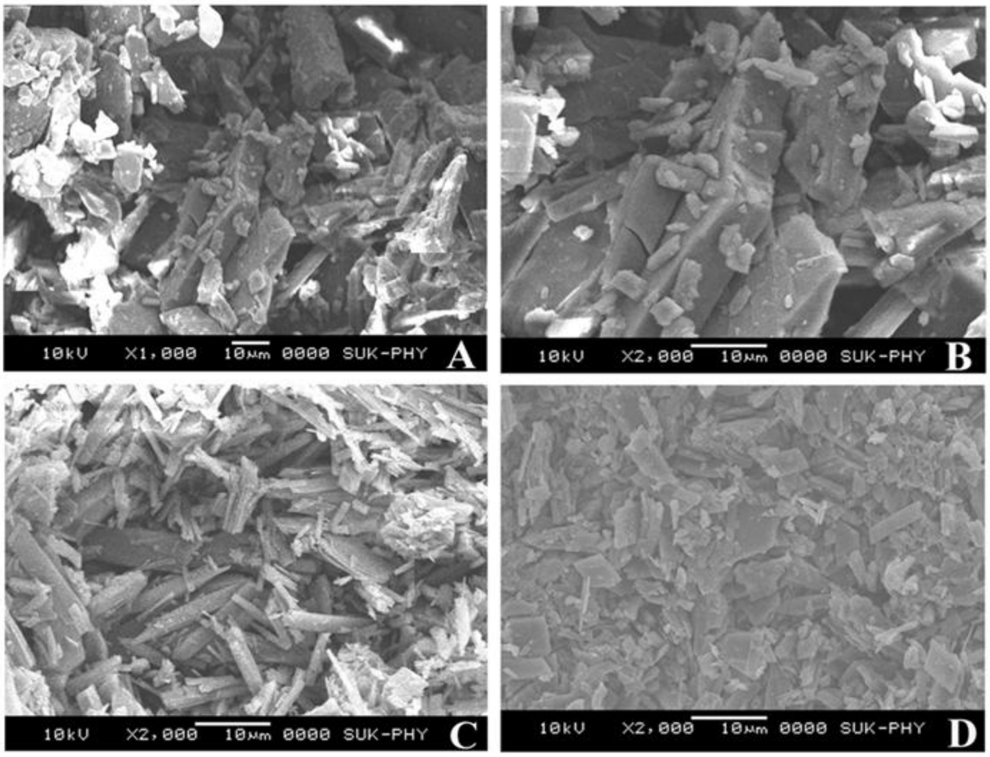

Figure 2: Scanning Electron microscopic photographs of A: Aceclofenac and Spherical agglomerates of ACF: B: Plane, C: with 1% PEG, D: with 2% PEG.

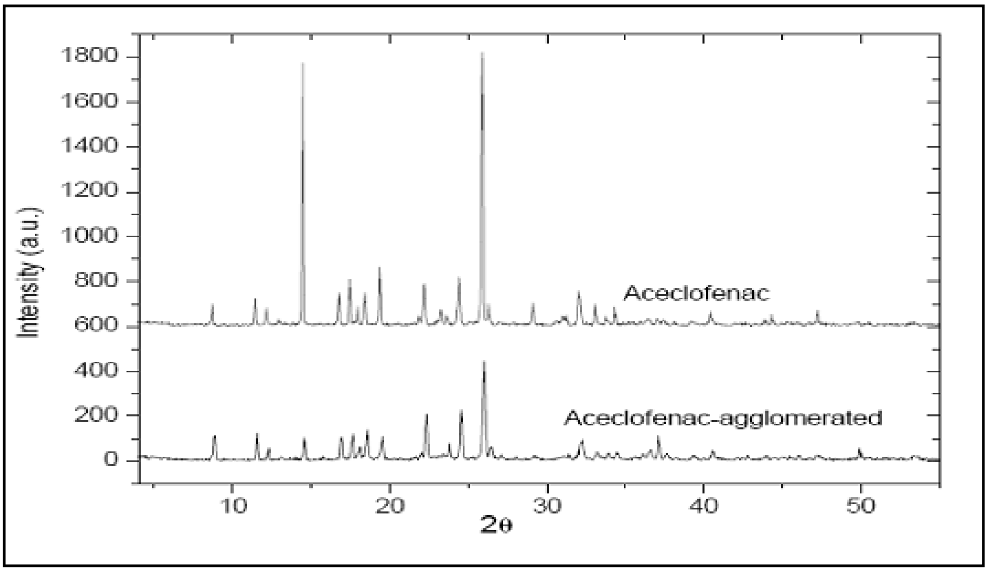

Figure 3: X-ray powder diffraction pattern of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000 (2%).

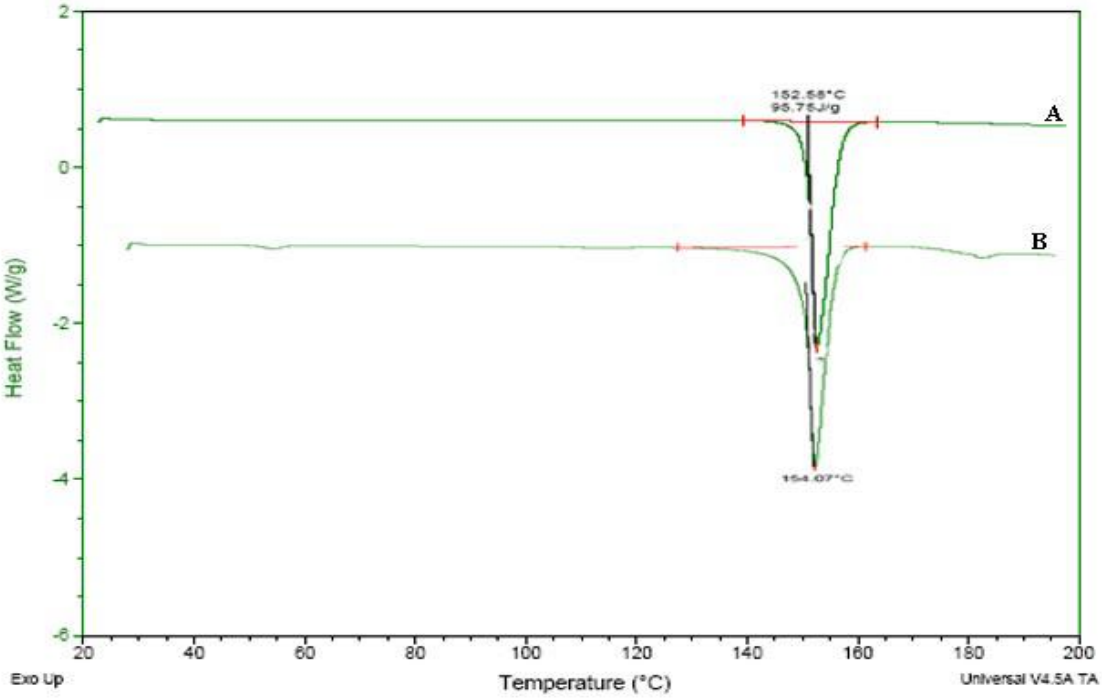

Figure 4: DSC thermograms of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000(2%).

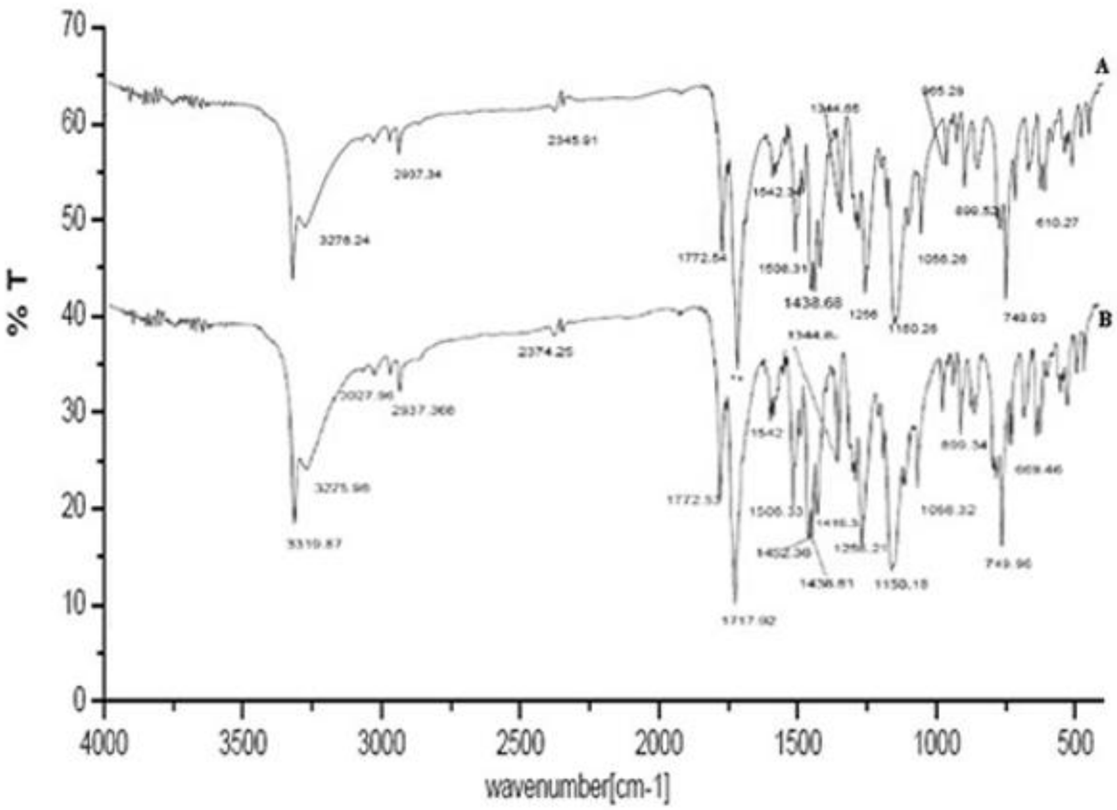

Figure 5: IR Spectra of A: raw crystals of ACF, B: ACF agglomerates with PEG 6000 (2%).

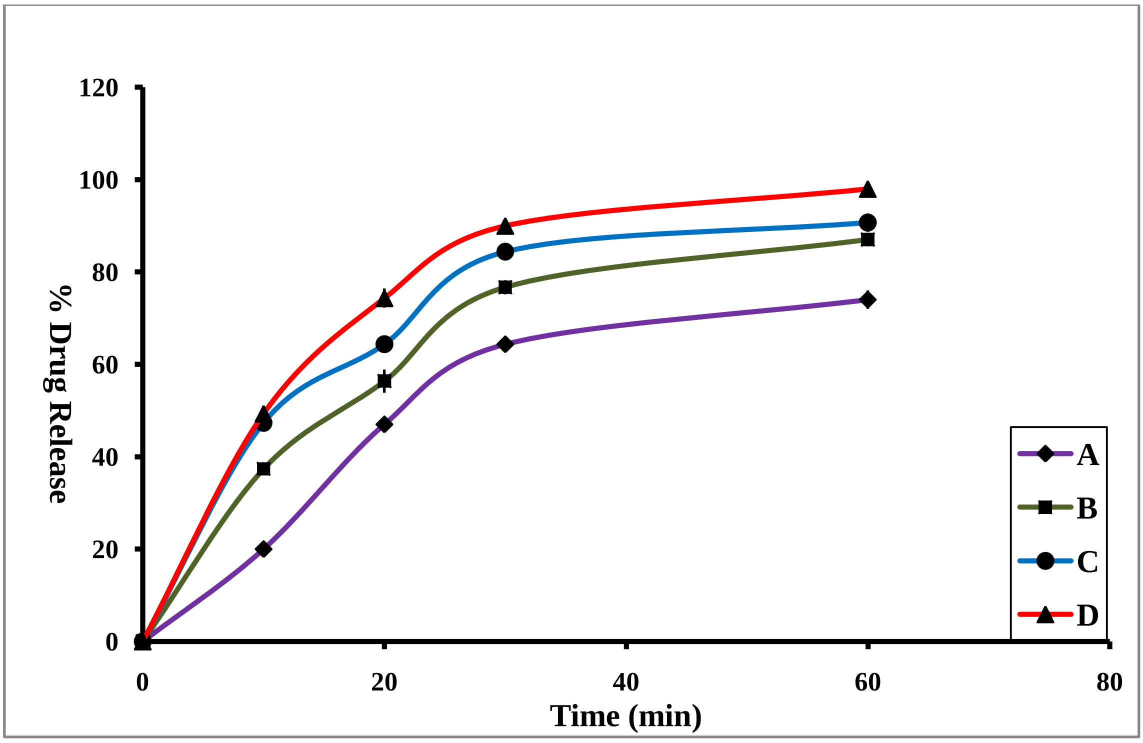

Figure. 6: Dissolution study of A: Aceclofenac and Spherical agglomerates of ACF: B: Plane, C: with 1% PEG, D: with 2% PEG

Table 1: Micrometric properties of raw crystals and spherical agglomerates of ACF.

Sample	Average diameter (µm) n=100	Angle of repose (°) (n=3)	Bulk density (g/cc) (n=3)	Tap density (g/cc) (n=3)	Carr's Index (%) (n=3)	Hausners ratio (n=3)
Raw crystals of ACF	16.7 ± 1.05	52.23 ± 0.75	0.322 ± 0.007	0.476 ± 0.006	32.35 ± 0.5	1.42 ± 0.04
ACF spherical agglomerates (Plane)	162.3 ± 1.13	23.14 ± 0.65	0.281 ± 0.006	0.331 ± 0.004	15.01 ± 0.4	1.18 ± 0.05
ACF spherical agglomerates with 1% PEG	152.8 ± 0.81	22.23 ± 0.75	0.279 ± 0.006	0.325 ± 0.003	14.15 ± 0.6	1.16 ± 0.04
ACF spherical agglomerates with 2% PEG	158.7 ± 1.19	23.23 ± 0.29	0.275 ± 0.008	0.320 ± 0.003	14.06 ± 0.7	1.16 ± 0.05

Table 2: Heckel parameters D_a, D_o, D_b, MYP (mean yield pressure) and ER (elastic recovery) of raw crystals and spherical agglomerates of ACF. (n=3)

Sample	D_a	D_o	D_b	MYP	% ER
Raw crystals of ACF	0.617 ± 0.003	0.416± 0.011	0.201± 0.007	22.54± 2.4	8.1 ± 1.2
ACF spherical agglomerates (Plane)	0.411 ± 0.002 **	0.173± 0.003 **	0.238± 0.005**	27.41± 1.8 **	4.8 ± 0.3 **
ACF spherical agglomerates with 1% PEG	0.564 ± 0.003 **	0.181± 0.004 **	0.383± 0.003 **	25.31± 1.6 **	5.1 ± 0.5 **
ACF spherical agglomerates with 2% PEG	0.483 ± 0.005 **	0.161± 0.008 **	0.322± 0.003 **	28.31± 2.3 **	5.0 ± 0.4 **

Significantly different from the value for raw crystals of ACF at p ? 0.001 (**)

Table 3: Solubility study of raw crystals and spherical agglomerates of ACF. (n=3)

Sample	Solubility (µg/ml) in Water
Raw crystals of ACF	30.8621 ± 1.2
ACF spherical agglomerates (Plane)	76.5086 ± 1.6 **
ACF spherical agglomerates with 1% PEG	82.9741 ± 2.1 **
ACF spherical agglomerates with 2% PEG	92.0603 ± 1.8 **

Significantly different from the value for raw crystals of ACF at p ? 0.001 (**)

Table 4: Stability study data of spherical agglomerates of ACF. (n=3)

Sample	0 Days		30 Days		60 Days		90 Days		180 Days	
	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)
Raw crystals of ACF	92 ± 2	96.3 ± 1	91 ± 2	95.7 ± 1	90 ± 2	94.8 ± 1	91 ± 1	96.1 ± 2	90 ± 1	94.9 ± 3
ACF spherical agglomerates (Plane)	94 ± 1	97.3 ± 1	93 ± 1	96.8 ± 1	92 ± 2	96.1 ± 1	92 ± 1	97.1 ± 1	91 ± 2	95.9 ± 2
ACF spherical agglomerates with 1% PEG	91 ± 3	98.6 ± 1	90 ± 2	98.4 ± 1	89 ± 3	97.6 ± 1	92 ± 1	98.1 ± 1	91 ± 1	96.8 ± 2
ACF spherical agglomerates with 2% PEG	92 ± 2	97.3 ± 1	91 ± 2	96.3 ± 1	92 ± 2	96.1 ± 1	92 ± 1	95.3 ± 2	90 ± 2	95.1 ± 1

No significant different from the values of 0 days as $p > 0.1$ for all agglomerates.

Source of Support: Nil.

Conflict of Interest: None declared

****