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Research Article

Improvement of Solubility and Compressibility of Ketoprofen by Melt Sonocrystallization.

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ABSTRACT

Melt-Sonocrystallization is a novel particle engineering technique having applications in pharmaceuticals. The present study was to investigate the suitability of the melt sonocrystallization technique in order to modify the processability properties along with solubility and drug release of non-steroidal antiinflammatory drug Ketoprofen which is class II drug. Melt sonocrystallized Ketoprofen agglomerates were prepared by probe ultrasonicator by varying the sonication time (1, 2 and 3 min) and level of amplitude (65, 75 and 85%). The melt-sonocrystallized Ketoprofen agglomerates were prepared at different time and amplitude, using probe ultrasonicator. The prepared agglomerates has shown an increase in the solubility and the drug release may be due to formation of porous agglomerates witnessed in Scanning Electron Microscopic photographs. These results were well supported by Differential Scanning Calorimetry and X-ray Powder Diffraction, which has indicated the decrease in drug crystallinity. As sonication time and amplitude increased, Study of Infra-red Spectroscopy revealed that no chemical transition of Ketoprofen has occurred during Melt sonocrystallization. Thus Melt sonocrystallization is a promising cost effective technique that may give a powder improved processability properties with improvement in solubility and drug release much needed for BCS class II drugs.

KEYWORDS

Ketoprofen, Melt Sonocrystallization, Solubility, Dissolution.

1. INTRODUCTION

Solubility and permeability of the drugs were decided factors for in-vivo drug absorption in pharmaceuticals. Physicochemical properties of drug crystals have a significant role in processability of drug during formulation and also in the therapeutic efficacy of drug. With the same intention most of particle engineering techniques are used to prepare drug crystals with desirable micromeritic and biopharmaceutical properties[1].Remarkable latest technologies are emerging in the field of pharmaceuticals for particle engineering focusing on simple standard formulations as economical as possible. In general fine crystals favour more attention over large crystals for high permeable and poor soluble pharmaceuticals considering better bioavailability. However, fine crystals often hamper powder processability parameters in formulation of solid oral dosage forms. Some of the prior technologies include spherical crystallization.

These technologies add positive approach in the development of BCS class II drugs as it contemplate on solubility enhancement, equally on powder processing parameters in the development of solid oral dosage forms. MSC is a novel particle processing technique, involves application of ultrasonic energy to the soft viscous or molten mass, dispersed in suitable dispersion media maintained at suitable temperature, with or without agitation during crystallization[2], extrusion spheronization[3], melt solidification[4], spray drying [5], pastillation[6] , solution atomization and crystallization by sonication [7], Where simultaneous crystallization and agglomeration occur. These technologies add positive approach in the development of BCS class II drugs as it contemplate on solubility enhancement equally on powder processing parameters in the development of solid oral dosage forms. Melt sonocrystallization (MSC) is a novel particle engineering technique, involves application of ultrasonic energy to the soft viscous or molten mass, dispersed in suitable dispersion media maintained at suitable temperature, with or without agitation having applications of ultrasonic energy during crystallization[8].It has been used to achieve nucleation at moderate super saturation during crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit. Several attempts have been made on applications of MSC on drugs like ibuprofen[9], celecoxib[10], naproxen[11], carbamazepine [12]. Fenofibrate (FNF) is anti-hyperlipidemic drug shows poor flowability, compaction properties along with poor dissolution. Various works were reported concerning about issues for solubility enhancement of FNF using melt granulation[13] and melt solidification[14] technique and also for compressibility improvement like spherical crystallization techniques[15].The present study deals with preparation and evaluation of melt sonocrystallized agglomerates of Keoprofen (MSC-KETO) to improve the compressibility along with solubility and drug release.

2. MATERIALS AND METHODS

2.1. Materials

Ketoprofen was purchased from Swapnroop Drug and Chemicals, Aurangabad, India. All other excipients were purchased from Unique Chemicals, Kolhapur, Maharashtra, India. All Chemicals used were of analytical grade.

2.2. Methods

Preparation of Melt-sonocrystallization Agglomerates:

The Ketoprofen (1gm) was melted using a water bath and the obtained molten mass was poured in a vessel containing 40 ml of deionized water at room temperature and sonicated for different time and amplitude, using probe ultrasonicator (Lab Quip Biologics, India) as given in table 1. The obtained product was collected by vacuum filtration, dried at room temperature and stored in a desiccator before use. The described process was repeated several times for obtaining enough material for characterization and for determining the repeatability.

Table 1: Different batches of formulation.

Formulation Codes	Amplitude (%)	Time (min)
K_1	65	1
K_2	65	2
K_3	65	3
K_4	75	1
K_5	75	2
K_6	75	3
K_7	85	1
K_8	85	2
K_9	85	3

2.3. Evaluation of MSC-KETO Agglomerates

Percentage yield and drug content:

Agglomerates were weighed after drying and percent yield was calculated as given in following formula.

$$\text{Percentage yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100$$

For determination of drug content MSC-KETO agglomerates equivalent to 100 mg of KETO were triturated and dissolved in phosphate buffer pH 6.8. Appropriately diluted samples were filtered through Whatman filter paper 41 (pore size 25 µm) and drug content was determined spectrophotometrically at 258 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). Percentage drug content was calculated using following formula

$$\text{Percentage drug content} = \frac{\text{Practical drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Micromeritic properties and Compaction behavior:

Mean particle size of pure KETO and all batches of MSC-KETO were determined by randomly counting average diameter of 100 particles with optical microscope. Bulk density, tap density,

Carr's index, Hausner's ratio and angle of repose were determined[1]. The compaction behavior of pure KETO and all batches of MSC-KETO were determined by the Heckel study.

$$\text{Hausners ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

$$\text{Carr's Index} = \frac{\text{Tap density}}{\text{Bulk density}} \text{Tap density} \times 100$$

2.4. Heckle Study

The study was performed by compressing 500 mg of pure KETO and all batches of MSC-KETO 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. Heckel parameters were determined using Heckle equation [16]. For determination of Elastic Recovery (ER) of pure KETO and all batches of MSC-KETO, thickness of the compact was determined at compression pressure 60 kN and at 24 hrs after releasing the tablet [17].

$$ER = [(t_2 - t_1) / t_1]$$

Where t_1 is the minimal thickness of the powder bed in the die and t2 is the thickness of the recorded tablet.

Crushing strength was measured immediately after compression with a tablet strength tester [18] (ErwekaTBH 30, Germany).

2.5. Solubility studies

Saturation solubility studies of KETO and all batches of MSC-KETO were performed in distilled water. Excess amount of sample was added to 25 ml distilled water and shaken for 24 hr using orbital shaker (Remi Instrument Ltd., Mumbai). Appropriately diluted samples were filtered through Whatman filter paper 41 (pore size 25 μm) and solubility was determined spectrophotometrically at 258 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

2.6. Scanning Electron Microscopy (SEM)

The samples of pure KETO and MSC-KETO (K_4) were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM; Cambridge, United Kingdom) operated at an acceleration voltage of 10 kV.

2.7. X-ray powder diffraction (XRPD)

X-ray powder diffraction of KETO and MSC-KETO (K_4) were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α–radiations (1.542A°) 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.

2.8. Differential Scanning Calorimetry (DSC)

Thermal properties of KETO and MSC-KETO (K_4) 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 30 to 300°C at a heating rate of 10°C/ min.

2.9. Fourier transforms Infrared spectroscopy (FTIR)

Fourier transforms Infrared spectroscopy of KETO and MSC-KETO (K_4) was recorded using Jasco V5300 (Jasco, Japan) FTIR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 400 to 2000 cm^{-1}

2.10. In-vitro Dissolution studies

The rate of dissolution of drug and MSC-KETO agglomerates was studied using USP 26 Type I dissolution test apparatus (VDA-8DR, USP, Veego, India). Sample equivalent to 100 mg KETO was placed separately in the dissolution vessel containing 900 ml pH 6.8 phosphate buffer maintained at 37 ± 0.5^0C and with 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (pore size 25 μm), concentration of KETO was determined spectrophotometrically at 258 nm on UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan).

2.11. Stability studies

All melt sonocrystallized of ketoprofen agglomerates were charged for the accelerated stability studies as required by the ICH guidelines (40 ± 2°C and 75 ± 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 aluminium caps. The samples were withdrawn at 30, 60, 90 and 180 days and evaluated for the drug content.

3. RESULTS AND DISCUSSION

Melt-sonocrystallization method here described appeared to be a suitable and simple technique to prepare agglomerates of KETO Yield, drug content and all micrometric properties of all batches were found satisfactory between 92 to 97 % w/w and 91 to 93 % respectively

3.1. Saturation Solubility

The solubility of KETO and MSC-KETO agglomerates which formed at different amplitude and sonication time are shown table 2.

Table 2: saturation solubility study.

Batch	Distilled water (mg/ml)*	Phosphate buffer pH 6.8 (mg/ml)*
Ketoprofen	0.04786±0.04	0.096±0.78
K_1	0.0718±0.007	0.271±0.004
K_2	0.0728±0.01	0.321±0.002
K_3	0.0842±0.08	0.613±0.021
K_4	0.117±0.03	0.831±0.03

K_5	0.192±0.05	0.789±0.11
K_6	0.201±0.12	1.011±0.02
K_7	0.293±0.09	0.992±0.09
K_8	0.312±0.13	1.229±0.041
K_9	0.328±0.04	1.722±0.021

The aqueous solubility of KETO was improved greatly. It was found that amplitude and sonication time increases, the solubility increased.

3.2. Heckel Study

As sonication time increased, particle size was found to be reduced. This may be due to the application of ultrasonic energy to the melted KETO, that leads to formation of smaller crystals due to super saturation and crystal growth that forms many nuclei, as resulted in reduction in particle size and surface roughness[9]. The flow properties of all MSC-KETO was improved compared to KETO, as indicated by the low angle of repose (< 40º), low compressibility index (< 25) and low Hausner's ratio (< 1.25). It has been observed that the amplitude has increased from 65 to 75%, Carr's index has drastically decreased but no significant difference was observed for 75 and 85%. The Heckel parameters D_b and MYP with ER are as given in Table 3. It was observed that D_b values of MSC-KETO are higher than pure KETO indicated. Fragmentation may be the dominant mechanism of compression although it was followed by plastic deformation. MYP for pure KETO was higher than MSC- KETO, which suggested that plastic deformation started earlier for MSC-KETO at lower compression pressure compared with pure KETO. Compactibility of samples was evaluated based on the tensile strengths of the compacts compressed at different compaction pressures.

The tensile strength of tablets prepared with MSC-KETO and raw crystals of KETO were plotted as a function of compression pressure shown in Figure1. It was found that the tensile strength of tablets with MSC-KETO were dramatically increased indicating enhanced fragmentation during compression resulting in increased Db. The elastic recoveries of the MSC- KETO compacts were smaller than the original drug crystals. These findings suggested that the MSC-KETO crystals were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression. The result has indicated that, as sonication time increased Db value has increased for 65 % amplitude, but for 75 and 85 % amplitude. The explanation is that the particle size decreased by increasing amplitude. Solubility of KETO was improved considerably up to 1.5 folds than native drug, as given in Table 2.

Table 3: Heckel parameters, Elastic recovery and solubility of KETO and MSC-KETO (n=3).

Batch Codes	**Heckel Constant D_b**	**Mean Yield Pressure (kN)**	**Elastic Recovery (%)**	**Solubility (mg/mL)**
Pure	0.209±0.004	31.90±0.03	7.1±1.1	0.04786±0.04

drug				
K_1	0.312±0.001	29.12±0.01	6.7±0.2	0.0718±0.007
K_2	0.345±0.002	31.25±0.04	5.3±0.1	0.0728±0.01
K_3	0.344±0.004	23.45±0.01	6.5±0.3	0.0842±0.08
K_4	0.351±0.005	22.12±0.02	5.2±0.6	0.117±0.03
K_5	0.289±0.001	19.36±0.08	5.7±0.4	0.192±0.05
K_6	0.324±0.003	32.38±0.03	4.3±0.5	0.201±0.12
K_7	0.366±0.004	28.45±0.09	5.7±0.8	0.293±0.09
K_8	0.378±0.001	26.34±0.12	5.5±0.1	0.312±0.13
K_9	0.458±0.002	31.22±0.012	5.8±0.2	0.328±0.04

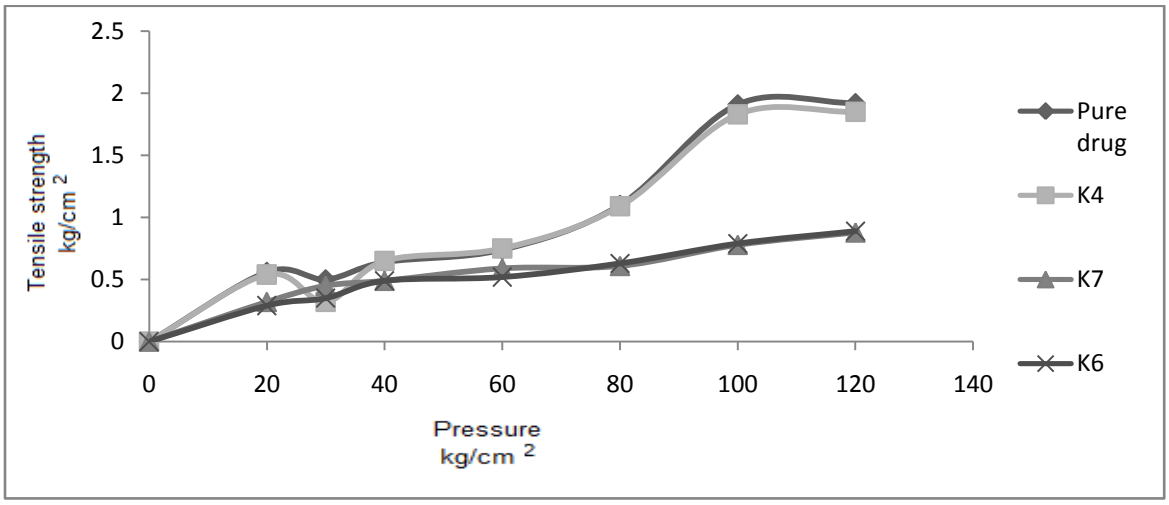

Figure 1: Tensile strength of tablets with MSC-KETO and raw crystals of KETO.

3.3. Scanning Electron Microscopy, FTIR, DSC and XRD

SEM image of pure KETO and MSC-KETO (K_4) is as shown the in figure 2. It has been observed that, as compared with KETO and MSC-KETO agglomerates were irregular in shape having rough surface with pores, some plates like structure and fines. This may be due to the micronization of the agglomerates by cavitation force of ultrasonication treatment.

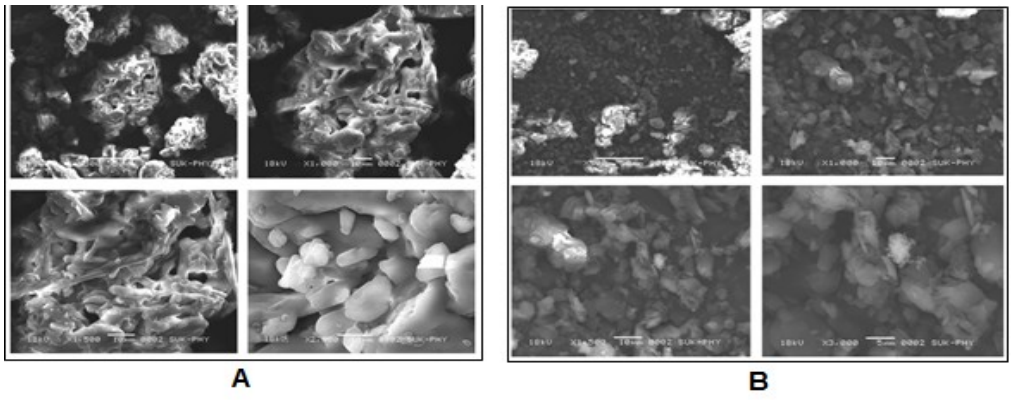

Figure 2: SEM images of A: Drug, B: Batch K_4

The FTIR spectrum, DSC and XRD pure drug of and optimized batch (K_4) is as shown in figure 3 and DSC in figure 4.

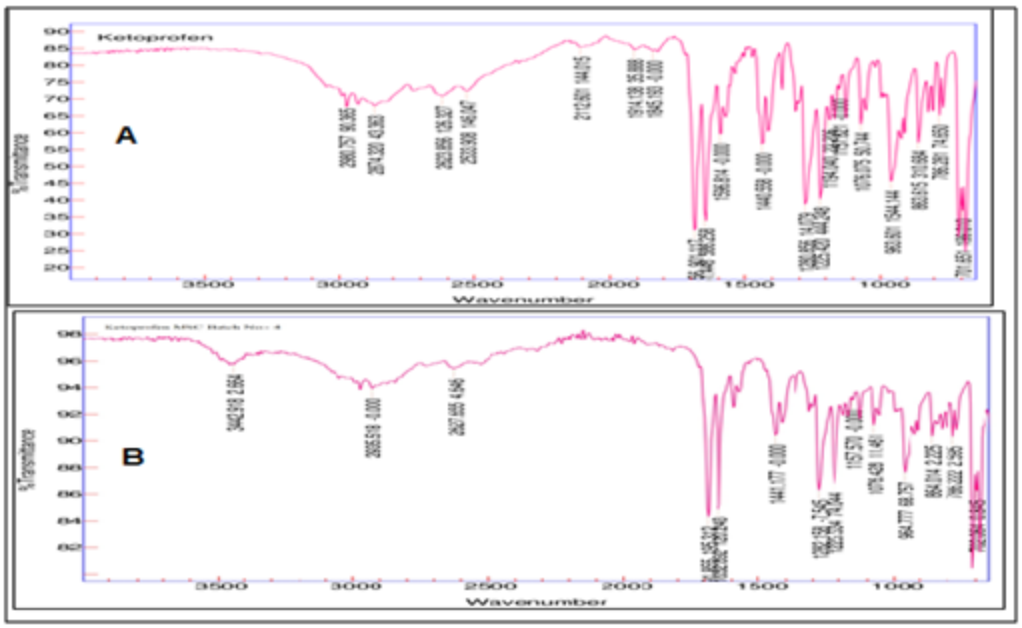

Figure 3: FTIR spectra of A: KETO B; Formulation batch K_4

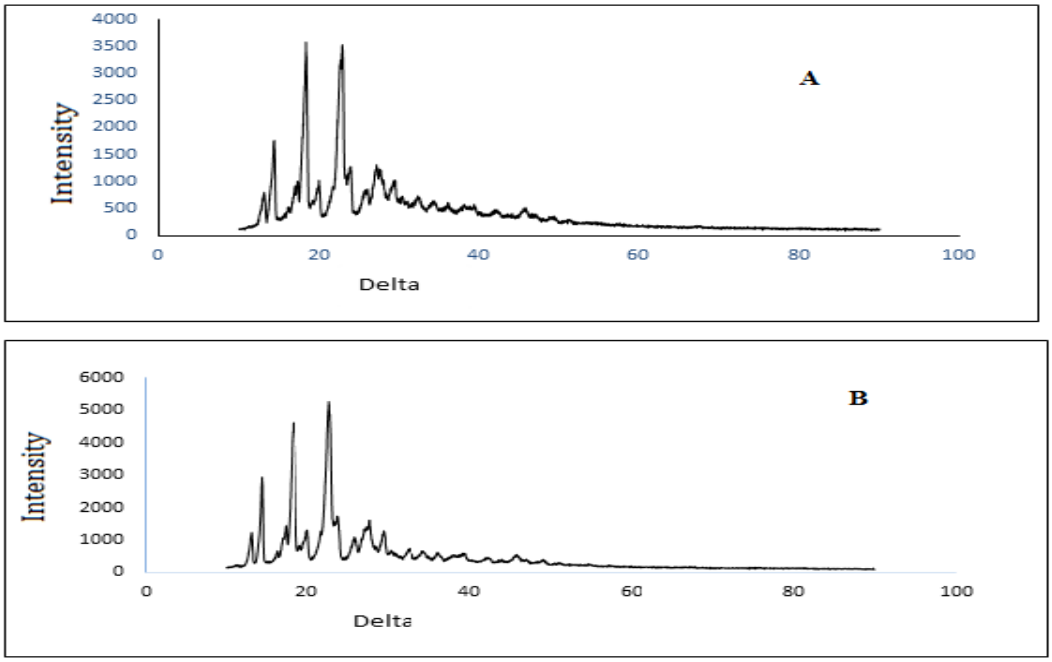

Figure 4: X-ray diffraction pattern of A is Ketoprofen & B is MSC KETO (K_4).

Differential Scanning Calorimetry Studies:-

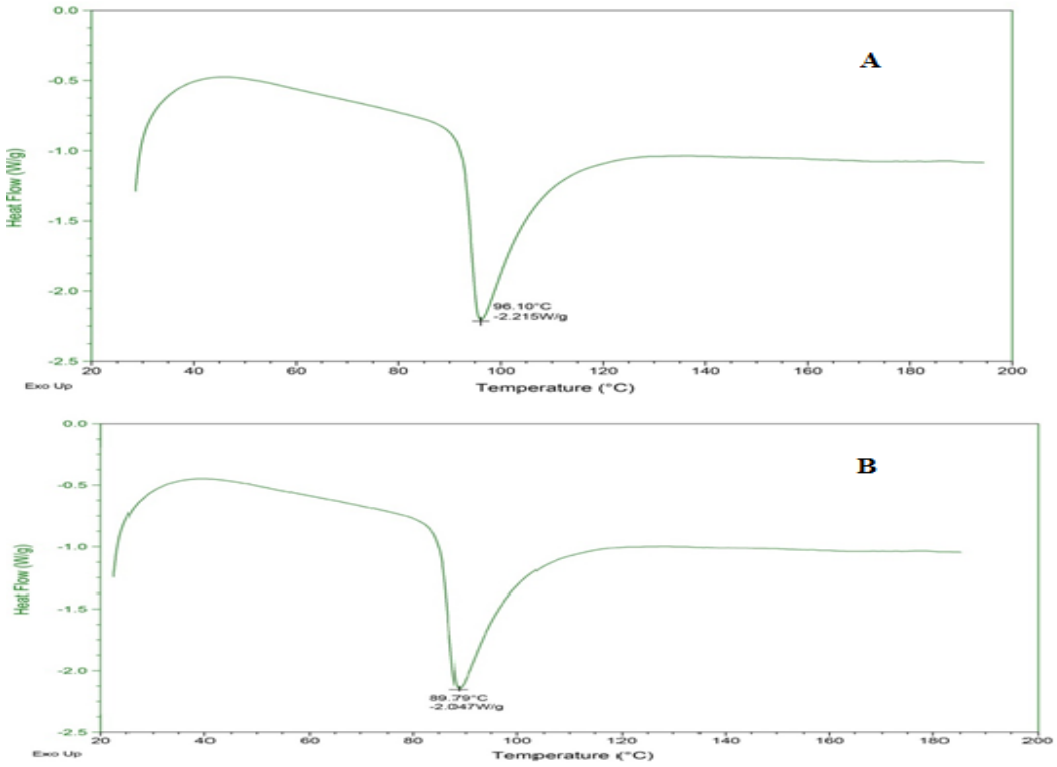

Figure 5. DSC Analysis of A is Ketoprofen and B is MSC K_4.

3.4. Drug Release Studies

The drug release studies in illustrate cumulative % drug release at 5 min, 10 min, 15 min, 20 min, 25 min, and 30 min of all formulated batches and pure drug. In figure 6 shows that the 65% amplitude agglomerates formulation batches (1, 2 and 3 minutes) compared with pure drug. It was found to be from drug release that, within 30 minutes the formulated agglomerates shows 80-90% drug was released in K_1 , K_2 and K_3 batches, which is more than of pure i.e. 30.18 % only 30% of pure drug released within 30 minutes. In figure no.6 shows that the 75 % amplitude agglomerates formulation batches (1, 2 and 3 minutes) compared with pure drug. It was found to be from drug release that, within 30 minutes the agglomerates shows 83-92% drug was released in K_4, K_5 and K_6 batches, which is more than that of pure drug i.e. 30.18 % only 30 % of drug released within 30 minutes. And in figure no.6, shows that the 85% amplitude agglomerates formulation batches (1, 2 and 3 minutes) compared with pure drug.

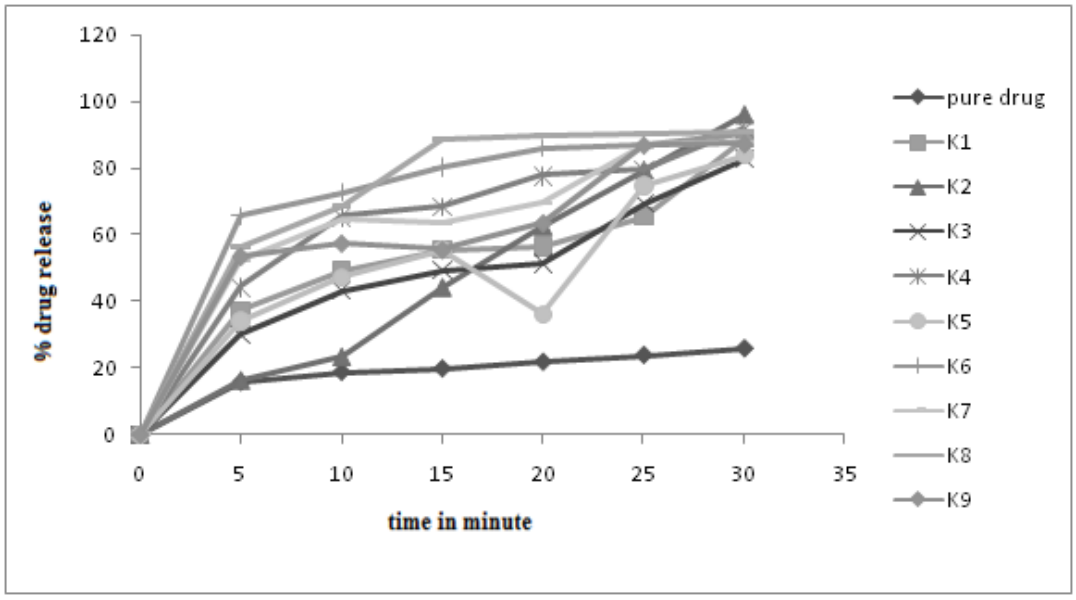

Figure 6: Pure drug and all Agglomerates batches drug release profile.

It was found to be from drug release that, within 30 minute the agglomerates shows 73-88 % drug was released in K_7, K_8 and K_9 batches, which is more than that of pure drug i.e. 26.04 % only 30 % of drug released within 30 minute. In work done the best optimized batch was found to be 75 %, 2 minute MSC agglomerates which shows highest drug release i.e. 91.92 %at 30 minute. The enhancement in dissolution rate may be due to particle size reduction, increment in the surface area and amorphization of drug and it was found to be that ultrasonic treatment has caused significant changes in the dissolution rate. The dissolution profiles presented in figure 6 illustrate the % drug release of KETO and MSC agglomerates of all batches with varying amplitude and sonication time i.e. 65 %, 75 %, 85 % amplitude with 1, 2, and 3 minutes respectively. The dissolution study was conducted in phosphate buffer pH 6.8 as a dissolution medium.[19,20,21] The batch was studied using micromeritic properties. SEM morphology of these batch was found that, as it is particle enlargement method, but particle size of powdered agglomerates size was found to be decreased as compared to pure drug, as process grows up, the average agglomerates size was found to be decrease with increase in sonication time, which might be due to breaking of agglomerates by ultrasound treatment.

4. CONCLUSION

The agglomerates of Ketoprofen were success prepared by melted sonocrystallization method. The agglomerates were irregular, with a rough surface, porous and showed improved micrometric properties and compressibility. Agglomerates showed improved solubility and dissolution rate, as compared with the native drug. Thus, it can be concluded that the prepared agglomerates of KETO by melted sonocrystallization technique may be a potential, reliable and effective tool for not only improved processability parameters, but also enhanced solubility and dissolution of drug.

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