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SPHERICAL CRYSTALLIZATION OF ZALTOPROFEN FOR ENHANCEMENT OF MICROMERITIC PROPERTIES AND DISSOLUTION RATE

E. Hari Krishna*[1], V. Ram Mohan Gupta [2] and S. Jyothi [1]

Department of Pharmaceutics, Shadan College of Pharmacy, Peerancheru, Hyderabad-08, Andhra Pradesh, India
Pulla Reddy Institute of Pharmacy, Dommadugu, Dundigal, Hyderabad, Andhra Pradesh, India

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Correspondence to Author:

E. Hari Krishna

HOD, Dept. of Pharmaceutics, Shadan College of Pharmacy, Peerancheru, Hyderabad-08, Andhra Pradesh, India

ABSTRACT

The present work deals with the spherical crystallization process by Spherical agglomeration method applied to Zaltoprofen, a novel NSAID drug. The object of present study was to prepare and characterize the spherical agglomeration of water insoluble non-steroidal anti-inflammatory drug. Zaltoprofen spherical agglomerates prepared with poly ethylene glycol, which is hydrophilic polymer by using simple spherical agglomeration technique for enhancing micromeritic properties and dissolution rate. The prepared zaltoprofen spherical agglomerates were examined in terms of flow properties, particle size analysis, compression and dissolution behavior. Physical characters of the crystals were studied for the morphology of crystals using scanning electron microscope (SEM), identification of polymorphism done by x-ray powder diffraction (XPRD) and for thermo dynamic properties using differential scanning colorimetry (DSC). The prepared agglomerates were improved the micromeritic properties, packability, wettability, solubility and compaction behavior, as well as dissolution behavior in comparison to pure Zaltoprofen drug.

INTRODUCTION: The conventional tableting method used involves first making granules and then compressing into tablets by way of direct (granule) tableting, but the need in recent years for process validation, GMP and automation of production processes has focused renewal of attention on the direct tableting, which involves few steps.

The direct compression is a modern technique in the tablet manufacturing, many processing steps are limited in direct compression and also wet granulation cannot be used with sensitive drugs [1]. Spherical agglomeration is a modern technique for development of directly compressible drugs where the drug crystals are converted to spherical form to improve flowability, compressibility, packability and to enhance dissolution rate characteristics of poorly water insoluble drug. Also direct tableting of pharmaceutical drugs is desirable to reduce the cost of production [2].

Spherical crystallization technique directly transforms the fine particles produced in the crystallization or in the reaction process into a spherical shape [3]. Agglomerates exhibit improved secondary characteristic like flowability and compressibility so that direct tableting is possible without further processing. The literature citation reveals that spherical crystals can be made in various ways such as Simple crystallization, Ammonia diffusion system method, Emulsion solvent diffusion method and Neutralization method. Out of these methods available to prepare spherical agglomerates, simple spherical crystallization is very easy, common and faster relative to other methods [4].

This technique as the name indicates, provides crystalline agglomerates which are spherical in shape, which exhibit excellent micromeritic properties of many drugs such as fenbrufen [5], ibuprofen [6], furosemide [7], indomethacin [8], aminophylline [9], enoxacin [10], tolbutamide [11], sulphamethoxazole [12], phenytoin [13] and norfloxacin [14].

Non-steroidal anti-inflammatory drugs are the most frequently prescribed preparations, Zaltoprofen is a novel NSAID drug exhibit poor flow and compression characteristics and hence it is a suitable candidate for spherical crystallization process to improve flow properties and compressibility. Further, Zaltoprofen shows incomplete and poor oral bioavailabilty due to low aqueous solubility [15], hence, in such case it is a valuable goal to improve therapeutic efficacy.

In the present study, it was planned to prepare spherical crystals of Zaltoprofen to increase the aqueous solubility, dissolution rate and bioavailability besides improving it micromeritic properties using PEG-6000 which is hydrophilic polymer [16].

MATERIALS: Zaltoprofen was obtained as a gift sample from M.S Hetero pharmaceutical, Hyderabad. Polyethylene glycol 6000 was obtained from S.D. Fine chemicals Mumbai. Dichloromethane, Acetone and Methanol were supplied from S.D. Fine chemicals Mumbai.

METHODS:

Preparation of Zaltoprofen Spherical Agglomerates: Spherical agglomeration of Zaltoprofen was prepared by simple agglomeration technique using three solvent systems. It involved a good solvent, a bad solvent and a bridging liquid. Acetone, dichloromethane and water were selected as good solvent, bridging liquid and poor solvent. These solvents were successfully used in previous studies.

A solution of Zaltoprofen (500 mg) in acetone (3 ml) was added to a solution of PEG 6000 (1-4% w/v) in 100 ml distilled water. The mixture was stirred continuously using digital mechanical stirrer (IKA motors. Mumbai) at 500 rpm, the bridging liquid (Dichloromethane; 0.5 ml) was added drop wise (**table 1**) and stirring was continued for 30 min.

The agglomerates were separated by filtration using Whatman filter paper (No. 1) and dried for 24 hours at room temperature.

TABLE 1: FORMULATION OF ZALTOPROFEN SPHERICAL AGGLOMERATES

Ingredients	F1	F2	F3	F4
Zaltoprofen (mg)	500	500	500	500
PEG-6000 (%)	1%	2%	3%	4%
Acetone (ml)	3	3	3	3
DCM (ml)	0.5	0.5	0.5	0.5
Water (ml)	100	100	100	100

Evaluation of Zaltoprofen Spherical Agglomerates:

1. **Shape:** The shape of the crystals was observed under optical microscope (10 magnification) attached to computer.

2. **Crystal density (ρ)**: It is the density of the actual solid material. This was determined by liquid displacement method by using 25 cc Specific gravity bottle with Toluene as immersion fluid. Three replicate determinations were made and the mean Calculated.

3. **Bulk density (ρ_b)**: It is defined as the mass of a powder divided by the bulk volume. This was determined by following the method [17]. A sample of 25.0 cc of powder from each batch, which has been previously lightly shaken in a closed container to break any agglomerates formed, was introduced into a 100 ml graduated cylinder. The cylinder was then dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density was thus obtained by dividing the weight of the sample in grams by the final volume in cc of the sample contained in the cylinder. Three replicate determinations were made and the mean calculated. (Remi Motors, Bombay, India)

4. **Tap density (ρ_t):** It is defined as the mass of a powder divided by the tap volume. A loosely packed volume of 25 cc of the powder from each batch was poured in a measuring cylinder by means of a funnel, after shaking lightly in a closed container. After observing the initial volume, the cylinder was mechanically raised and allowed to fall under its own weight on a hard surface from a height of 2.5 cm at the rate of 120 taps per minute, until no further change in the volume was

observed. The tap density was calculated by dividing the weight of the sample in grams by the final volume in c.c. of the sample contained in the cylinder. Three replicate determinations were made and mean calculated.

5. **%Compressibility (%C):** Carr derived [18] this dimensionless quantity which proves to be useful to the same degree as that of angle of repose values for predicting the flow behavior. The more compress a material is, the less flowable it will be and the less compressibility, the more flowable. Compressibility indirectly gives an excellent picture of uniformity in size and shape, cohesion and moisture content. The formula used was,

$$\%\text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

The computed values for the different batches of crystals were expressed in percent and tabulated.

6. **Hausner`s ratio** [19]: Particles with high interparticulate friction or cohesiveness have Hausner's ratio greater than 1.6 and % compressibility values higher than 40, whereas powder with Hausner's ratio less than 1. 2 and % compressibility between 5 to 17 can be classified as free flowing powders. Hausner's ratio was calculated using following formula;

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

7. **Porosity:** The state of packing of a powder is described by its porosity, which is defined as the ratio of the void volume to the bulk volume of the packing.

$$\text{Porosity} = \frac{\text{Bulk volume - Tapped volume}}{\text{Bulk volume}} \times 100$$

Porosity is frequently expressed in percent. Porosity values were computed for all batches using the formula.

8. **Angle of repose (ϕ):** Angle of repose was determined for all the batches as an index of flow behavior using basically, the method suggested by Philpel [20]. The height H and mean radius r measured from five different directions were used to calculate the angle of repose, using the formula,

$$\text{Angle of Repose } (\phi) = \tan^{-1} H / r$$

Five replicate determinations were made in similar conditions of relative humidity and mean angle of repose values were calculated.

9. **Scanning Electron Microscopy:** The surface morphology of the agglomerates was assessed by scanning electron microscopy (Lexica stereo Scan S-3700; Cambridge, UK).

10. **Drug Content Determination:** The drug content of the crystals was determined by dissolving 80 mg of crystals in 100 ml of methanol followed by measuring the absorbance of appropriately diluted solution spectrophotometrically. (Pharmaspec UV-1700, UV-Visible Spectrophotometer, Shimadzu, Tokyo, Japan) at 340 nm.

11. ***In-vitro* Dissolution Studies:** The *in-vitro* dissolution studies were carried out using 8 station USP XXIII dissolution testing apparatus (Electrolab, Mumbai, India). The dissolution medium used was 900 ml, mixture of phosphate buffer solution pH 6.8 and water (1:1) used as dissolution medium [21]. The agglomerates containing 80 mg of zaltoprofen were weighed and then introduced into the dissolution medium. The medium was stirred at 50 rpm using paddle at 37±0.5°C. The samples were collected, filtered through Whatman filter paper (0.45um) and analyzed spectrophotometrically at 340 nm.

RESULTS AND DISCUSSION: Spherical Agglomerates of Zaltoprofen were prepared by simple spherical agglomeration, which involves a good solvent, a poor solvent and bridging liquid. From the solubility data of Zaltoprofen, the solvents are selected since Zaltoprofen is highly soluble in acetone, insoluble in water, acetone selected as good solvent, water as poor solvent and dichloromethane as bridging liquid as the dichloromethane has good wettability with the drug and immiscible with the water. The percentage of drug content of the prepared agglomerates showed between 93% to 97% shown in **Table 2**.

TABLE 2: PERCENTAGE DRUG CONTENT OF ZALTOPROFEN SA

Spherical crystals	Drug content (%)
PEG 6000 (1%)	95.75 ± 1.25
PEG 6000 (2%)	93.89 ± 2.26
PEG 6000 (3%)	95.61 ± 2.12
PEG 6000 (4%)	97.32 ± 1.29
ZALTOPROFEN(pure)	100.00 ± 0.00

Micromeritic Properties:

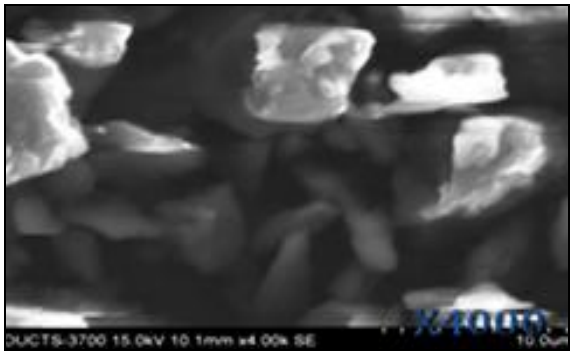
Flow properties, Porosity and Density: The flow properties of zaltoprofen spherical agglomerates were studied in term of Hausner's ratio, Carr's Index and Angle of repose, which were mentioned in table 3. The Carr's index significantly reduced by the spherical agglomerates (10.0 to 10.2) than that of pure drug (42.0) which indicates significant increase in flow rate of the agglomerates. Hausner's ratio of agglomerates was less than 1.2, which indicates improved flowability of agglomerates. Angle of repose of spherical agglomerates falls between 22 to 29, among the four formulations F4 had reduced angle of repose indicates better flow properties, this may be the significant reduction in interparticle friction because of the good spherical shape and larger size of the spherical agglomerates. The percentage of the porosity of agglomerated crystals showed significantly higher as compared to the raw crystals of zaltoprofen, increased porosity improves the wettability and dissolution rate at little extent.

From the bulk, granular, and true density of the agglomerated crystals, the results indicated that all densities of the agglomerated crystals showed decrease value because of the increased in volume and the total porosity of agglomerated crystals (**Table 3**).

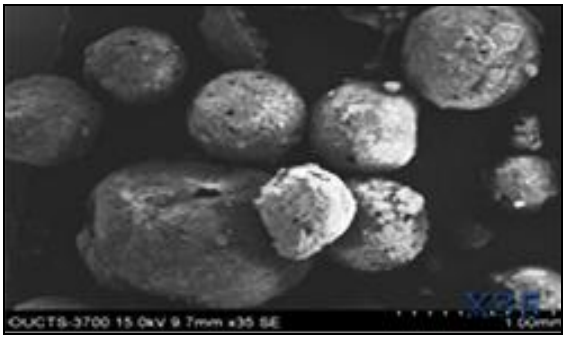
TABLE 3: MICROMERITIC PROPERTIES OF ZALTOPROFEN SPHERICAL CRYSTALS PREPARED IN THE PRESENCE OF DIFFERENT CONCENTRATIONS OF PEG-6000 AND PURE DRUG

Spherical crystals	LBD (g/ml)	TBD (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose	True Density (g/ml)	Porosity (%)	Particle size (µm)
F1	0.42±0.01*	0.45±0.01*	10.20±1.51*	1.18±0.01*	29.31±1.23	1.22±0.12	59.55±2.36	201.12±10.18*
F2	0.40±0.02*	0.45±0.01*	10.10±2.36*	1.10±0.02*	26.47±2.31	1.25±0.26	65.15±2.16	218.13±12.10*
F3	0.37±0.01*	0.41±0.01*	10.00 ±2.12*	1.10±0.01*	25.61±1.89	1.28±0.10	71.05±3.01	230.25±11.77*
F4	0.39±0.01*	0.44±0.01*	10.10±2.69*	1.00±0.01*	22.88±1.65	1.25±0.16	74.32±1.36	235.11±12.23*
Pure Drug	0.30±0.01	0.52±0.02	42.00±2.36	1.69±0.03	42.61±1.99	1.55±0.46	55.50±2.21	85.55±10.25

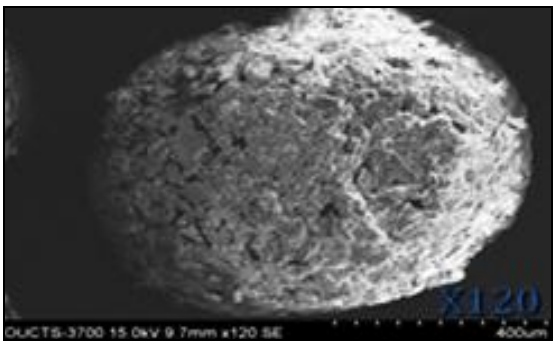
Scanning Electron Microscopy: The results of surface morphology studies were shown in SEM **Fig. 1**. The parent zaltoprofen crystals were in the form of fine needles, which is in confirmation with the earlier report. This long-needle form of zaltoprofen leads to very poor flow and compressional difficulties. The prepared agglomerates were spherical to larger extent and remaining was irregular in shape with smooth surface, which enabled them flow very easily.



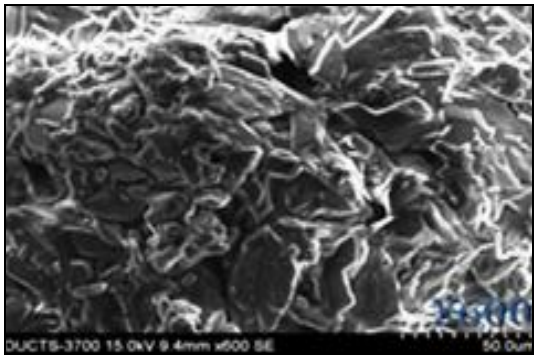
1A



1B



1C



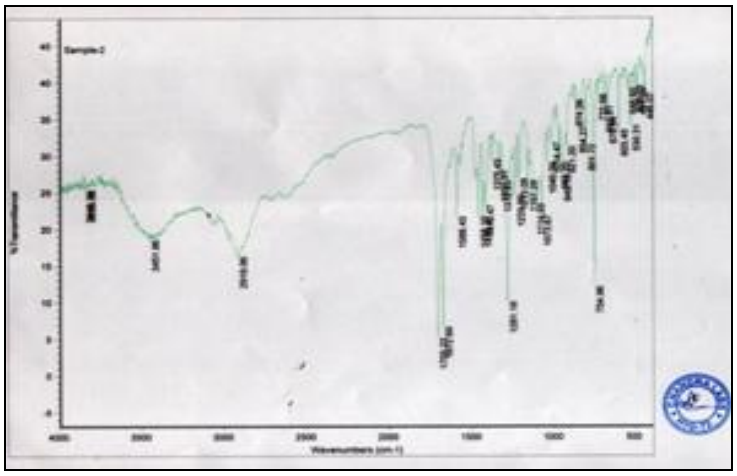
1D

FIG. 1(A) SEM MICROGRAPH PURE ZALTOPROFEN, 1(B),(C),(D) SEM MICROGRAPHS OF SPHERICAL AGGLOMERATES F4.

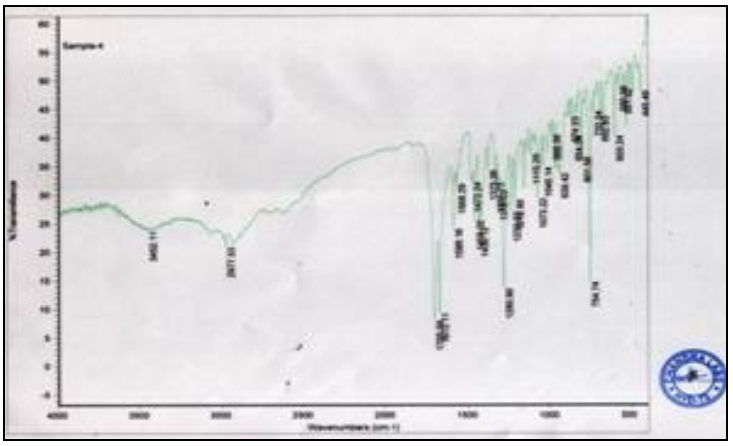
FTIR Spectroscopy: IR spectroscopy and DSC studied the possible interaction between the drug and the carrier. The interaction often leads to identifiable changes in the IR profile and melting point of drug. The principal IR peaks of pure zaltoprofen and IR peaks of spherical agglomerates were shown in **Table 4, Figure 2 (A), (B)**. No considerable changes were observed in the IR peaks of crystals when compared to pure zaltoprofen. These observations indicate the absence of well-defined interaction between zaltoprofen, PEG 6000 and other additives used in the crystals.

TABLE 4: FTIR PEAK OF PURE DRUG AND PEG SPHERICAL CRYSTALS

Samples	Major peaks (Wave numbers), cm^{-1}
Pure Zaltoprofen	1705.08, 1672.58, 1588.29, 1458.11, 1014.06, 603..34
Spherical Crystals (4% PEG 6000)	1705.59, 1672.11, 1588.16, 1458.02, 1040.14, 603.24



2A

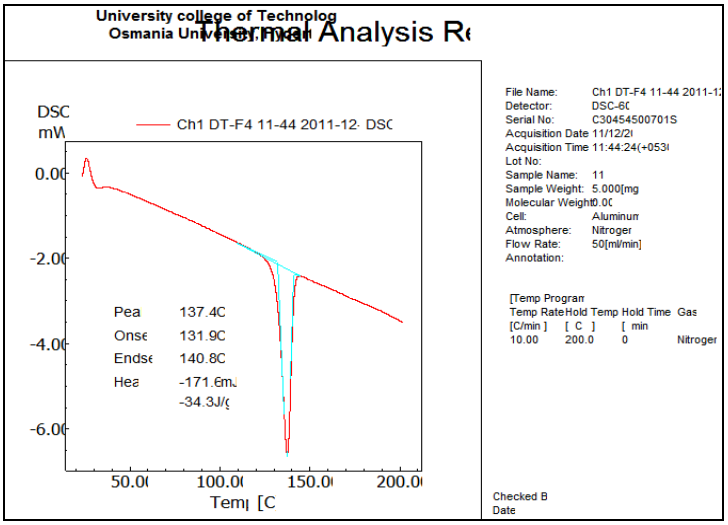


2B

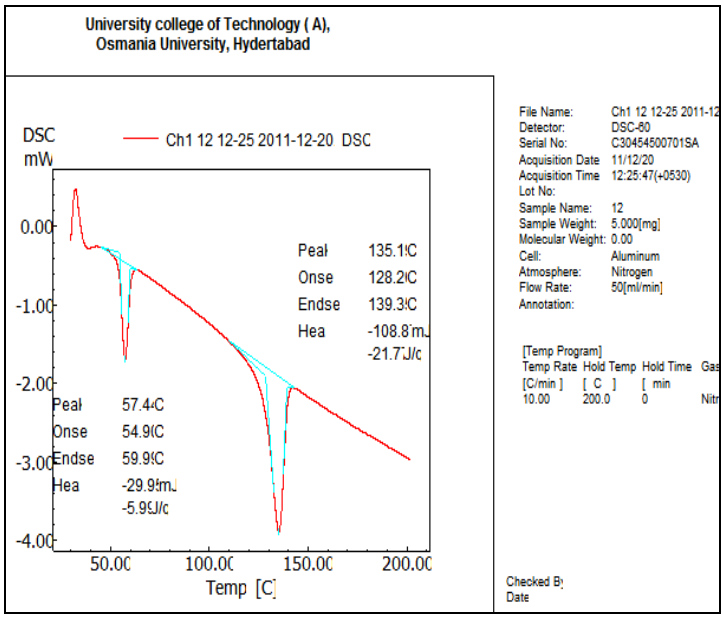
FIG. 2: IR SPECTRA OF A) ZALTOPROFEN B) SPHERICAL AGGLOMERATES F4.

Differential Scanning Calorimetry Studies: The DSC thermograms of pure zaltoprofen and its crystal forms were shown in **Fig. 3 (A), (B)**. Pure zaltoprofen showed a sharp endotherm at 140.81°C corresponding to its melting point. Zaltoprofen spherical crystals showed sharp endotherm at 139.3°C. There was negligible change in the melting endotherms of the spherical crystals compared to pure drug. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between drug, PEG 6000 and additives used in the preparation. However, there was a decrease, although very little, in the melting point of drug in spherical crystals compared to that of pure zaltoprofen.

FTIR spectra and DSC studies of agglomerates showed that, the drug was stable in the prepared formulations indicating the absence of interaction between zaltoprofen and hydrophilic polymers.



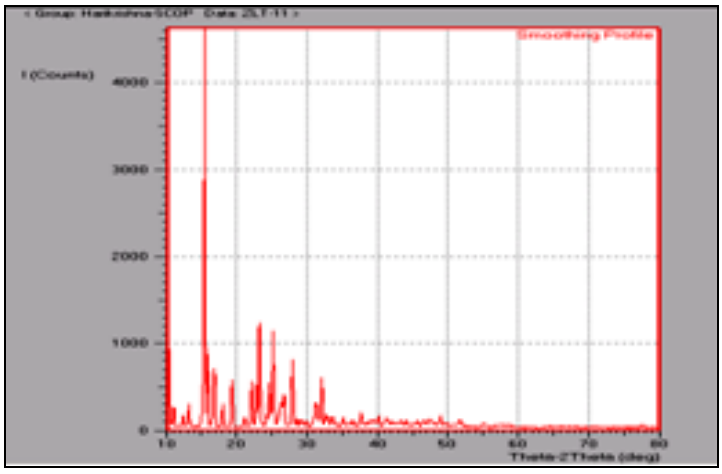
3A



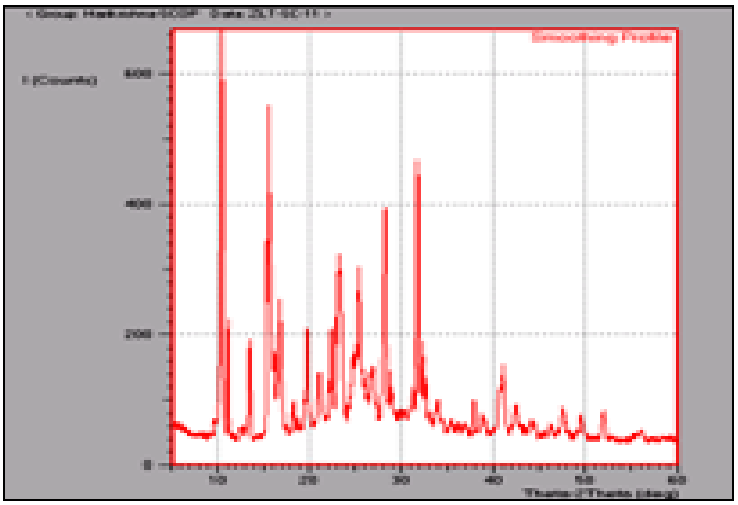
3B

FIG. 3 DSC PATTERNS OF; A) ZALTOPROFEN; B) SPHERICAL AGGLOMERATE F4

X-Ray Diffraction Studies: Comparison of powder X-ray diffraction spectra of zaltoprofen and spherical agglomerates indicate considerable decrease in crystallinity of spherical agglomerates. After the recrystallization, no polymorphic phenomenon was detected, as all powder X-ray diffraction patterns of primary crystals consisting of agglomerates were consistent with the pattern of original crystals. The decrease in crystallinity of the drug indicates increase in amorphous nature the drug, which may increase in the solubility of the drug. After the recrystallization, no polymorphic phenomenon is detected using X-ray diffractometer as all powder X-ray diffraction patterns of the primary crystals consisting of agglomerates were consistent with the pattern of original crystals **Fig. 4(A), (B)**.



4A



4B

FIG. 4 (A, B): X-RAY DIFFRACTION STUDIES

Dissolution studies: From the results of solubility and dissolution studies, the spherical agglomerates prepared from PEG 6000 (4% w/v) showed maximum solubility and drug release in water compared to pure drug and other batches of spherical agglomerates. As **Fig. 5** indicates F4 was dissolved 84.4% in 30 min where pure drug dissolved 60.6% in 30 min time. The results revealed that the spherical agglomerates with 4% w/v PEG 6000 significantly increases the drug release compared to the pure drug.

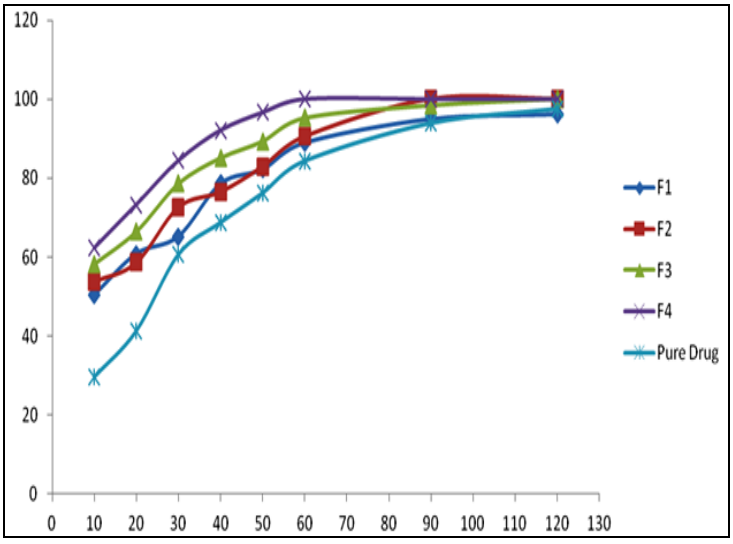


FIG. 5: DISSOLUTION STUDIES

CONCLUSION: The spherically agglomerated crystals of zaltoprofen were successfully prepared for direct tableting by the spherical agglomeration technique. The micromeritic properties of agglomerates such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tableting.

The main factor in the improvement of flowability and packability was due to their spherical shapes and smooth surfaces. The agglomerates have shown improved *in-vitro* drug release performance comparable with untreated zaltoprofen. Therefore, from the above it can be concluded that spherical crystallization is a tool of particle engineering, which can transform the poorly flowable drug powder into spherical crystals, those are best suited for direct compression. The conversion of poorly flowable powder into spherical agglomerates enhances the speed of tableting because of elimination of most of steps, which required in the wet granulation and in dry granulation process.

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