Preparation and Evaluation of Direct Compressible Fenofibrate Spherical Agglomerates.

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Abstract

Present study related to the formulation of directly compressible fenofibrate (FNO) spherical agglomerates. Spherical agglomerates were prepared by using a three solvent system comprising methanol: dichloromethane: water (good solvent, bridging solvent & bad solvent respectively). The effect of speed of rotation and amount of bridging solvent on spherical agglomeration were studied. The agglomerates were subjected to various physicochemical evaluations such as practical yield, drug content, solubility, flowability, packability, compactibility, wettability, crushing strength, scanning electron microscopy, FTIR spectroscopy, differential scanning calorimetry, X-ray powder diffraction studies and dissolution studies. The spherical agglomerates showed improved micromeritic properties as well as dissolution behavior in comparison to pure drug. Spherical agglomerates were found to be a better in solubility and *in-vitro* dissolution. This study, demonstrated that the successful development of direct compressible FNO spherical agglomerates.

Key Words

Fenofibrate, spherical agglomerates, solubility, direct compression, tablets, *In-vitro* dissolution.

Introduction

Spherical agglomeration is the novel technique that can directly transfer the fine crystals produced in the crystallization or in the reaction process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transfer crystals directly into a compacted spherical form. There are many active pharmaceutical ingredients in pharmaceutical market with unfavorable flowability, solubility, and compressibility due to their irregular crystal habit. Poor compressibility of a specific crystal habit of drug can be attributed to the presence of crystal faces that give poor adhesion to each other and absence of the faces that are required for optimal adhesion. In 1986, Kawashima *et al.* used the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Spherical crystallization was defined by Kawashima as "an agglomeration process that transfers crystals directly to compact spherical forms during the crystallization process."

It also enables co-precipitation of the drug and the encapsulating polymer in the form of a spherical particle[1]. This technique of particle designing of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size, and particle size distribution) can be modified during the crystallization process. As a consequence of such modifications in the crystal habit, certain micrometric properties (bulk density, flow property, and compactibility) and physicochemical properties (solubility, dissolution rate, bioavailability and stability) can also be modified. It had been described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compressibility of some powders. Moreover, critical steps involved in wet granulation can be avoided. This technique involves selective formation of agglomerates of crystals that are held together by liquid bridges. This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried out more efficiently. Furthermore, the resultant agglomerated crystals could be easily compounded

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with other pharmaceutical powders due to their spherical shape[2]. It is a simple process and inexpensive enough for scaling up to a commercial level, which reduces time and cost by involving faster operation, less machinery, and fewer personnel, with great advances in tabletting technology, especially the introduction of a number of directly compressible excipients. Using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical processing like milling, mixing, and tabletting because of their excellent flowability and Packability[3]. Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvents, i.e. good solvent–bridging liquid–poor solvent. When bridging liquid plus good solvent of API are poured into the poor solvent under agitation, quasi-emulsion droplets of bridging liquid or good solvent forms the emulsion droplets in the poor solvent and induces crystallization of the drug followed by agglomeration. Fenofibrate (FNO) (isopropyl ester of 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoic acid) is a widely used hypolipidemic drug. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to the Biopharmaceutics Classification System (BCS), FNO is a Class II having low solubility and high permeability. Bioavailability of FNO solely depends on dissolution rate in the gastrointestinal tract. This drug is used mostly in lipid regulation as it decreases low-density lipoprotein (LDL) and very-lowdensity lipoprotein (VLDL) levels, and increases highdensity lipoprotein (HDL) level[22].

Materials and Methods

Materials

FNO was obtained as a gift sample from Alembic Research Ltd., Vadodara, India, Analytical chemicals like methanol and dichloromethane were obtained from Loba Chemicals, Mumbai, India.

Preparation of FNO spherical agglomerates

FNO spherical agglomerates were prepared by Quasi-emulsion solvent diffusion system (QESDS). 10 g of FNB was dissolved in the mixture of 40 mL methanol (good solvent) and 10 mL dichloromethane (bridging liquid), thermally controlled at 25°C so as to form the saturated solution of the drug. The solution was poured into 200 mL of distilled water (poor solvent) with a stirring rate of 500 ± 50 rpm using a propeller type of agitator at room temperature. After agitating the system for 15 min, the prepared agglomerates were collected by filtration through Whatman filter paper No. 42 under vacuum. The spherical agglomerates were washed with distilled water and placed at 45°C for drying in a hot air oven for 24 h and then stored in a desiccator[6,7].

Evaluation of spherically agglomerated crystals

FNO spherical agglomerates Detection of drug content

Equivalent to 160 mg of FNO were accurately weighed, crushed and transferred to a 100 mL volumetric flask. To this, 50 mL of methanol was added and sample was sonicated for 20 min so as to dissolve the drug. The volume was made up to 100 mL with methanol and filtered through a 0.45 μm filters. The filtrate was diluted with methanol and analyzed at 290 nm by uv-spectrophotometer (Shimadzu, Tokyo, Japan). The study was performed in triplicate (n = 3).

Solubility study

Solubility studies were carried out using deionized water as a solvent. Excessive quantity of FNO and its spherical agglomerates were taken in screw-capped test tubes with a fixed volume (10 mL) of deionized water. The resulting suspension was treated at room temperature with 100 rpm in an incubator shaker. After 24 h, the samples were withdrawn and filtered through 0.45 μm filters. The filtrate was diluted with deionized water and analyzed at 290 nm by uv-spectrophotometer (Shimadzu, Tokyo, Japan). The study was performed in triplicate (n = 3).

Dissolution study of spherical agglomerates

In-vitro dissolution studies were carried out with FNO and its spherical agglomerates. Each test was carried out in United States Pharmacopoeia dissolution apparatus II (paddle) consisted of 1000 mL, 0.05 M sodium lauryl sulfate in deionized water maintained at 37.0 ± 0.5°C and stirring at 50 rpm. An accurately weighed quantity of each sample equivalent to 160 mg of FNO was subjected to the test. Samples 5 mL were withdrawn at predetermined time interval (10, 20, 30, 45 & 60 minutes) and immediately replace with the equal volumes of dissolution medium. Samples were filtered and appropriately diluted with methanol.

Diluted samples were analyzed at 290 nm by uv-spectrophotometer (Shimadzu, Tokyo, Japan).

Flow property

Flowability of FNO and its spherical agglomerates were determined in terms of the following parameters: Bulk density, Tapped density, Hausner ratio, Carr's index and Angle of repose[10].

Packability

Packability was assessed by analysis of the tapping process with the Kawakitas (I) and Kunos (II) method and using the parameters a, b, and k in the equation:

$$N/C = 1/(ab) + N/a \quad \text{----------------------(I)}$$

Where, C = (Vo – Vn)/Vo, a = (Vo – V∞)/Vo, N = number of tapping, C = difference in volume (degree of volume reduction), a and b = constant for packability and flowability, Vo = initial volume, Vn = final volume after nth tapping, and V∞ = powder bed volume at equilibrium.

The slope 1/a and intercept 1/ab of plot N/C verses N gives the compactibility a, constant of flowability b, and cohesiveness 1/b.

$$\rho f – \rho n = (\rho f – \rho o). \exp. (–kn)\text{----------(II)}$$

Where ρf, ρo, ρn are apparent densities at equilibrium, initial state, and nth tapped respectively. The value of k in Kunos equation was determined directly putting the values of the densities[11,12].

Heckel analysis

Heckel analysis is expressed as:

$$\ln (1/(1-D)) = kP + A$$

Where D is the relative density of a powder compact at pressure P. Constant k is a measure of the plasticity of a compressed material. Constant A is related to the die filling and particle rearrangement before deformation and bonding of the discrete particles. The Heckel analysis was made using tablets prepared at compaction pressure between 20 MPa and 120 MPa, in a hydraulic press using 13.00 mm flat faces punches. At every pressure applied, the diameter, height, and weight of the tablets were measured. The density (D) at every pressure was divided by the real density measured in a helium picnometer (QuantaCrome Foran, USA) and relative density (D) was calculated. Where D is the relative density of the compact at pressure P, k is the slope of the linear portion of the plot, and A is a function of the initial bulk volume (intercept on a Heckel plot). Constant A is related to the die filling and particle rearrangement at nil pressure. The slope (k) of the Heckel equation provides information about the compaction mechanism of a substance. Mean yield pressure (Py) was calculated as the inverse of the slope (1/K) expressed in MPa.

Powder bed hydrophilicity study

FNO and its spherical agglomerates (0.5 g) were placed on a sintered glass disk forming the bottom of the glass tube. The whole device was brought into contact with water and adjusted at 1 mm under the surface of water. Some methylene blue crystals were put on the surface of the drug. The time taken for the capillary rising of water to the surface was noted. This time was visualized by the dissolution of methylene blue crystals with the color of the powder surface intensively. The shortest rising time would correspond to the most hydrophilic substance, leading to good wettability[13]. The study was performed in triplicate (n = 3).

Crushing strength

It was measured using a 50 ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel was then used as a hallow support and the guide tube was used with close fitting tolerances to the plunger. The hallow plunger with an open end served as the load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of the granule on the base plate. The plunger acted as a movable plate and was set directly on the granules positioned on the lower plate as the rate of loading may affect the crushing load (g). Mercury was introduced from the reservoir into the upper chamber at the rate of 10 g/s until the single granule crushed. The loading time was < 3 min. The total weight of the plunger and the mercury required to fracture a granule was the crushing load. A minimum of 10 granules were tested and the average load in grams was taken as the crushing strength[14]. The study was performed in triplicate (n = 3).

Characterization of spherically agglomerated crystals

Scanning electron microscopy (SEM)

The shape and surface morphology of plain FNO and its spherical agglomerates were studied by scanning

electron microscopy (JEOL, JSM 50A, Tokyo, Japan).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry analysis was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. Samples of plain FNO and its spherical agglomerates were heated in sealed aluminum pans under nitrogen flow (30 mL/min) at a scanning rate of 5 °C/min from 20 °C to 150°C. Empty aluminum pan was used as a reference.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000-400 cm-1. The procedure consisted of dispersing samples plain FNO and its spherical agglomerates in KBr and compressing into disc by applying pressure of 5 tons in 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

X-ray powder diffraction (XRD)

X-ray diffraction pattern of plain FNO and its spherical agglomerates were recorded using Philips X-ray diffractometer (Model: PW 1710) with copper target at 30 kV voltage and 30 mA current. The scanning speed was 1° per minute.

Results and Discussion

Optimization of agglomeration process

On the basis of solubility data available of FNO, methanol, dichloromethane and water were selected as good solvent, bridging liquid and bad solvent, respectively. Selection of the bridging liquid should be such that it should be immiscible with the poor solvent i.e. water and the drug should have slight solubility in it. The method used for the preparation of spherical agglomerates was the quasi-emulsion solvent diffusion system (QESDS) in which droplets of the solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible and crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets. Various spherical agglomerates were prepared to select optimum speed of rotation. The impact of agitation speed on formulation of spherical agglomerates was such that on increase in agitation speed beyond 500 ± 50 rpm, spherical agglomerates with smaller diameter and rough surface were produced. Fine powder was present along with irregular shaped agglomerates,

which could be due to high shear force of stirrer. The agglomerates with good spherical shape and flowability were produced at agitation speed of 500 ± 50 rpm. When the agitation speed was reduced to 400 ± 50 rpm, large irregular agglomerates were produced, where the shear energy may not be sufficient for the formation of good crystals.

Evaluation of spherical agglomerates of FNO

The practical yield of spherical agglomerates prepared was 92.39 % and drug content was observed 98.54 %. Aqueous solubility of drug was improved by spherical agglomeration method. The aqueous solubility study was carried out in deionized water. Spherical agglomerates of FNO showed improved aqueous solubility (0.14 ± 0.02 mg/mL) as compared with aqueous solubility of plain FNO (0.08 ± 0.01 mg/mL). This may be due to changes in the crystal forms because of different habit, structure, and surface modification. And, in some instances, solvents included into the crystal forms solvets or clathrates that change the surface properties and the reactivity of the drug particles and the internal energy of the molecules, playing an important role in increasing solubility[18]. Flowability of the spherically agglomerates was studied in terms of bulk density, tapped density, Carr's index, Hausnar ratio and angle of repose. Plain FNO crystals have a significantly higher angle of repose (39.13 ± 2.31 %) in comparison with the spherical agglomerates (Table 1), which could be due to the irregular shape of the crystals, which hindered in the uniform flow of crystals from the funnel. The reason for the excellent flowability of spherical agglomerate is the significant reduction in the interparticle friction because of the perfect spherical shape and the larger size of the crystals. The Carr's index revealed that the flowability of the FNO was significantly poor than that of the spherical agglomerates, i.e. spherical agglomerates had a lower Carr's index than plain FNO (45.16 ± 0.32 %). The Hausnar ratio of the spherical agglomerate was found to be less than 1.25, which also indicates improvement in the flowability of the agglomerated crystals[19]. The packability profile of the spherical agglomerates from Kawakitas equation showed a significantly smaller value of parameter (a), (1/b) and a significantly higher value of parameter (b) as compared with plain FNO (Table 1). Kunos equation showed that spherical agglomerates have a significantly larger value of parameter k. From the

values of all these parameters, it is proved that the spherical agglomerates showed a higher packability than that of plain FNO. The increasing packability of the spherical agglomerates may be due to the lower surface and the wider particle size distribution of the spherical crystals. During the tapping process, smaller particles might have infiltrated into the voids between the larger particles and resulted in improved packability[20]. Heckel analysis has been used to classify powders as their compaction behavior and for the interpretation of the mechanism of bonding. Mean yield pressure (Py) is the pressure required to deform a powder or granules and to obtain compacts and is defined as the inverse of slope of the linear portion of the Heckel plot. The slope (k) is an indication of the deformation behavior of the material. With low values of Py, the amount of plastic deformation increases and when high values of Py is an indication of the material compressing behavior is mainly fragmentation[24]. The values obtained from Heckel equation as shown in Table 1 indicated significant low mean yield pressure (Py) of spherical agglomerates than plain FNO resulted in good compaction behavior of spherical agglomerates as compare to plain FNO. Powder bed hydrophilicity study revealed that the spherical agglomerates showed a significantly shorter rising time of water to its surface as compared with plain FNO and the crushing strength of spherical agglomerates is significantly more than that of the Plain FNO granules as shown in Table 1.

Dissolution study

In *In-vitro* dissolution study results showed (Figure 1) significant faster drug release profile of spherical agglomerates (58.3 %) as compared with plain FNO (41.8 %) in 60 minutes. The reason for this faster drug dissolution was linked to the increase in surface area FNO due to spherical agglomeration, better wettability of the spherically agglomerated crystals and also because of spherical agglomerates has a more porous internal structure exhibit a faster drug release rate than those of the less-porous agglomerates[21].

Characterization of spherically agglomerated crystals

Plain FNO and its agglomerated crystals showed plain FNO were irregular shaped as compared with the agglomerated crystals, which were spherical in shape and were composed of minute needle-like crystals indicating the polymorphism or solvation would have occurred during the agglomeration process (Figure 2). The prominent IR peak (wave number cm-1) of FNO and spherical agglomerates are shown in Figure 3. The IR spectra of all the tested samples showed the prominent characteristic peaks of plain FNO which confirm that no chemical modification of the drug has been taken place. The XRD scan of plain FNO showed intense peaks of crystallinity, whereas the XRD pattern of spherical agglomerates exhibited halo pattern with less intense and denser peaks compared with plain FNO indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form (Figure 4). This further supports the DSC results which demonstrated partial amorphization of the drug in agglomerates. In the DSC studies, plain FNO showed a sharp endotherm at 81.34 °C corresponding to its melting point (Figure 5). There was no appreciable change in the melting endotherm of spherical agglomerates to that of pure drug. This observation also confirmed the absence of chemical interaction of the drug with additives during agglomerate process, further supporting the results of FTIR spectroscopy. The DSC results also indicates little amorphization of FNO when prepared in the form of spherical agglomerates. This is evident by a decrease, although little, in the enthalpy changes of agglomerates when compared with that of pure drug, also may be attributed to the variation in crystallinity due to the alteration in the packing arrangement of the molecules in the crystals and the altered hydrogen bonding.

Conclusion

Present study concluded that spherical agglomerates of FNO prepared by the QESDS showed an improvement in the solubility, dissolution rate, packability, compactibility, wettability, flowability and crushing strength also showed excellent physico-chemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

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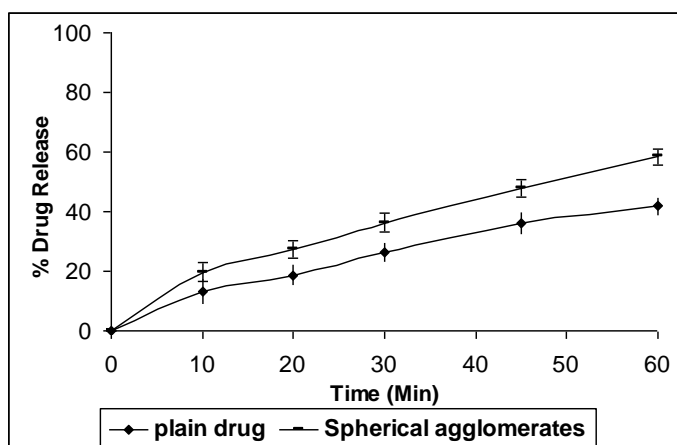
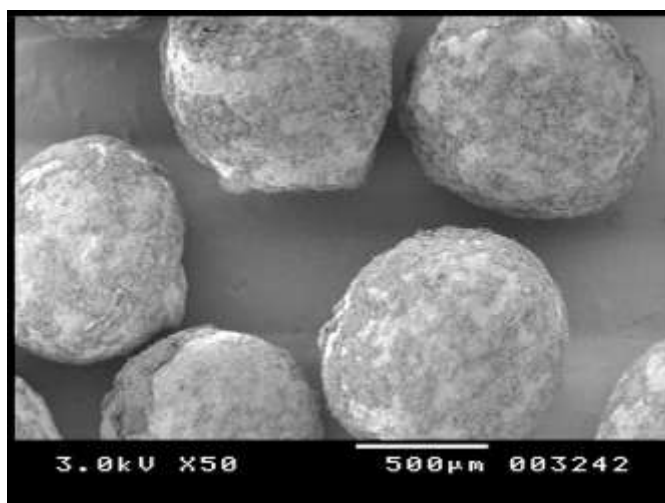**Figure 1:** Dissolution profile of FNO & its spherical agglomerates.

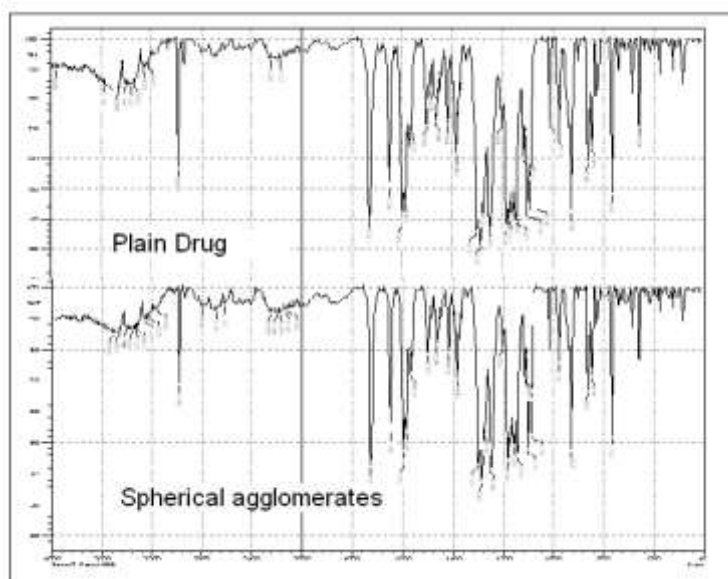**Figure 2:** SEM of spherical agglomerates of FNO.

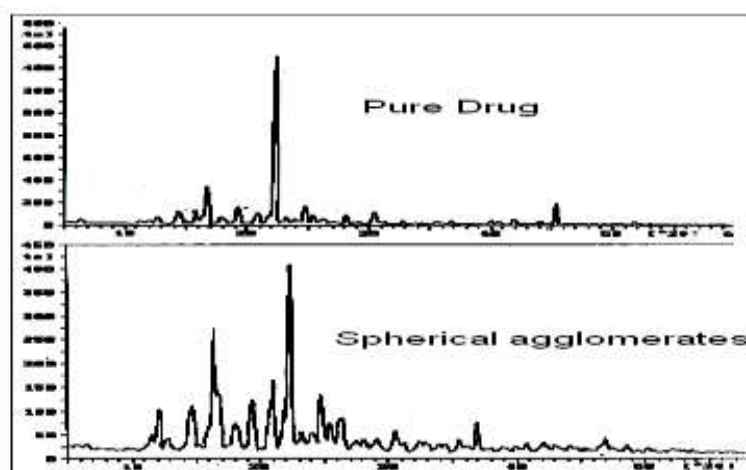**Figure 3:** FTIR spectra of FNO & its spherical agglomerates.

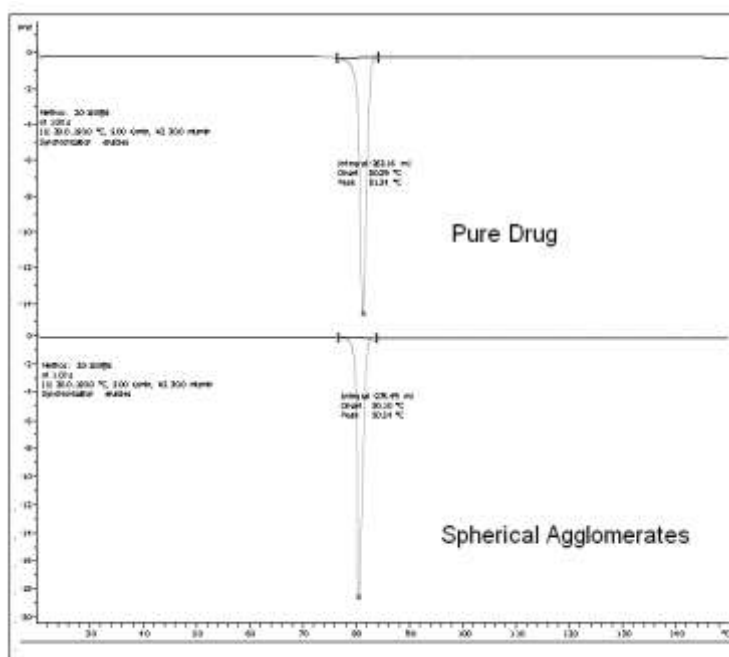**Figure 4:** XRD Pattern of FNO & its spherical agglomerates

Figure 5: DSC thermograms of FNO & its spherical agglomerates.

Table 1: Evaluation parameters of FNO and its spherical agglomerates.

Parameters	FNO	FNOAGG
Practical yield (%)	-	92.39 ± 0.83
Drug content (%)	99.71 ± 0.16	98.54 ± 0.28
Aqueous solubility (mg/mL)	0.08 ± 0.01	0.14 ± 0.02
Wettability (h)	16 ± 0.41	13 ± 0.37
Angle of repose (°)	39.13 ± 2.31	21.28 ± 1.56
Bulk density (g/mL)	0.34 ± 0.04	0.52 ± 0.03
Tapped density (g/mL)	0.52 ± 0.03	0.63 ± 0.04
Carr's index (%)	45.16 ± 0.32	17.46 ± 0.61
Hausner ratio	1.82 ± 0.08	1.21 ± 0.01
Crushing strength (g)	-	28.73 ± 0.28
a	0.92 ± 0.32	0.21 ± 0.27
b	0.001 ± 0.02	0.005 ± 0.04
1/b	851.67 ± 9.27	181.81 ± 8.95
k	0.014 ± 0.01	0.023 ± 0.01
Py	52.81 ± 4.63	32.28 ± 6.24

All the values represents mean ± S.D. (n = 3).

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