Preparation and Characterization of Spherical Agglomerates of Piroxicam by Neutralization Method

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ABSTRACT

Piroxicam, an anti-inflammatory drug, exhibits poor water solubility and flow properties. The aim of the present study was to develop piroxicam spherical agglomerate and was prepared by neutralization method. Crystallization medium used for spherical agglomerates of piroxicam consisted of 1 N sodium hydroxide; 0.07M HCl, chloroform (bridging liquid) in the ratio of 25:67:8 mL, respectively. Spherical agglomerates were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. Micromeritic and mechanical property and dissolution behavior studies were carried out. Process variables such as amount of bridging liquid, stirring time and duration of stirring were optimized. Dissolution profile of the spherical agglomerates was compared with pure sample and recrystallized sample. The samples were stored in stability chamber to investigate their physical stability. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties then pure piroxicam. The dissolution of the spherical agglomerates was improved compared with pure sample and recrystallized sample. Dissolution of spherical agglomerates showed higher %release i.e., 63.42% in 60 min compare to other pure piroxicam i.e. 38.17%. In stability test, the release profile of the spherical agglomerate was almost unchanged as compared with the freshly prepared spherical agglomeration stored at 20°C and 45% relative humidity for 90 days. Hence this technique can be used for formulation of tablets of piroxicam by direct compression with directly compressible tablet excipients.

Key words: Spherical agglomerates, piroxicam, crystallinity, dissolution, direct compression

INTRODUCTION

Piroxicam is a derivative of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAID). It is a 4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1, 2-benzothiazine- 3-carboxamide-1,1-dioxide, a white slightly yellow and crystalline powder and is practically insoluble in water, with a molecular weight of 351.56 (Vreec et al., 1991; Alpaslan et al., 1997). In the case of individuals who suffer from rheumatoid arthritis and related painful joint disorders, the Non-Steroidal Anti-Inflammatory Agents (NSAIDs) may be more effective at relieving pain (Balamuralidhara et al., 2011). It is widely used in the treatment of inflammation and pain associated with rheumatic disorders such as rheumatoid arthritis, osteoarthritis and in soft tissue injury. Piroxicam is also widely used to treat postoperative pain and fever in children (Dix et al., 2004; Labrousse et al., 1989).
Formulation and manufacture of solid oral dosage forms and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression (Singh et al., 2011). Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tabletting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets (Shangraw, 1989). In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder (Gharaei-Fathabad, 2011). Spherical agglomerates is one of such techniques to improve the micromeric properties and dissolution of drug (Kawashima, 1984).

Spherical agglomeration process is a multiple unit process in which crystallization, agglomeration and spheronomization can be carried out simultaneously in one step (Chourasia et al., 2004). The resultant crystals can be designated as spherical agglomerates (Paradkar et al., 1994). Due to the characteristic shape, the micromeric properties such as flowability, packability and compressibility of the resultant crystals are dramatically improved, so that direct tableting or coating is possible without further processing (e.g., mixing, agglomeration, sieving, etc.) (Bose and Heerens, 1982).

Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The properties of the particles so designed vary greatly as compared to the fine crystalline material (Espitalier et al., 1997). These agglomerates were found to have good flowability and compressibility. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs (Kawashima et al., 1984). These modifications allow for the practice of more efficient manufacturing methods that could save time and reduces economic risk (Kulkarni and Dixit, 2010a). Piroxicam exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties (Dixit et al., 2010). Various methods were used to increase the flow properties of poorly water soluble drugs, e.g., coating, granulation etc.

The objective of the present study to prepare spherical agglomerates of piroxicam by neutralization method and were evaluated for DSC, FT-IR, XRD and SEM analysis were performed to determine the physicochemical properties of the spherical agglomerates and compare with recrystallized sample and pure drug and determined the solubility and dissolution characteristics of the piroxicam spherical agglomerates and investigate their physical stability in a climate chamber at 20°C and 45% Relative Humidity (RH) for 90 days.

MATERIALS AND METHODS
Piroxicam was obtained as a gift sample from IPCA Lab. Mumbai., India. All chemicals and buffers used were of analytical grade.

This study, has been done from first October 2010 to fifteen February 2011.

Preparation of spherical agglomerates of piroxicam: Piroxicam (2.5 g) was dissolved in 25 mL 1 N sodium hydroxide heated at 45°C until a clear solution was obtained. The drug solution was quickly poured in to 67 mL of 0.07 M HCl maintained at 20°C, under continuous stirring.
at 600 rpm with a propeller. When fine crystals of piroxicam begun to precipitate (about 2 to 3 min), 5 mL of chloroform was added. After 2 min 3 mL of chloroform was added again. After 5 min of stirring spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45°C for 12 h. The spherical agglomerates were kept in a desiccator's room temperature until further experiment.

Reccrystallization of piroxicam: Piroxicam (2.5 g) was dissolved in 25 mL 1 N sodium hydroxide heated at 45°C and 8 mL of chloroform was added. The drug solution was poured quickly in to 67 mL of 0.07M HCl maintained at 20°C with occasional stirring. The crystals of piroxicam were collected by filtration and were dried at 45°C for 12 h.

Determination of residual solvents concentration in spherical agglomerates: Gas chromatography (Shimadzu GC-14B chromatograph) was used to estimate residual of chloroform in spherical agglomerates. The column used was DB-624 (6% cyanopropyl phenyl and 94% dimethyl polysiloxane) which was having a length of 30 m and internal diameter of 0.53 mm. The detector used was FID using helium as carrier gas and nitrogen as pure gas. The flow rate for hydrogen was maintained at 60 kpa equivalent to 50 mL min⁻¹ and for nitrogen at 100 kpa equivalent to 40 mL min⁻¹. The flow rate in the column was kept at 30 kpa equivalent to 4.29 mL min⁻¹ and the temperature was maintained at 260 and 220°C for detector and capillary injector, respectively. Column temperature was maintained 120°C for 8 min and the temperature was gradually raised to 220°C at the rate of 30°C per min.

Drug content: Spherical agglomerates (50 mg) were triturated with 10 mL of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 mL. Five millilitres of this solution was mixed with equal volumes of methanol and phosphate buffer pH 7.2 to produce 100 mL. Absorbance of the resulting solution was measured at 334 nm. Drug content was determined from standard plot.

Differential scanning calorimetry (DSC): A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 1 mg of piroxicam or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL min⁻¹) at a scanning rate of 10°C min⁻¹, from 25 to 250°C. An empty aluminum pan was used as reference.

Fourier transform infrared (FTIR) spectroscopy: The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 mg of the pure drug, recrystallized and spherical agglomerates were used separately. Pure drug, spherical agglomerates and recrystallized samples were dispersed in KBr powder and the pellets were made by applying 6000 kg cm⁻² pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis: X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. X-Ray powder diffraction patterns were obtained at room temperature using a Philips X’ Pert MPD diffractometer, with Cu as anode material and
graphite monochromator, operated at a voltage of 40 mA, 45 kV. The samples were analyzed in the 20 angle range of 3-50 and the process parameters used were set as scan step size of 0.0170 (20), scan step time of 51.0362 sec and time of acquisition of 1 h. The 20 values were processed using multidimensional minimization programme to calculate cell volume, cell parameters and space grouping.

Scanning Electron Microscopy (SEM): Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

Micromeritic properties: Particle size of recrystallized samples and pure samples were determined by microscopic method using calibrated ocular micrometer and size of spherical agglomerates was determined by sieving method. Apparent particle densities of agglomerated and unagglomerated crystals were measured using a Pycnometer. Carr’s index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electrolab, Mumbai). The angle of repose of agglomerated and pure crystals was measured by fixed funnel method.

Mechanical properties: Tensile strength of spherical agglomerates was determined by compressing 500 mg of crystals using hydraulic press at different kg cm⁻² for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (o) of the compact (kg cm⁻²) was calculated using following equation:

\[ o = \frac{2F}{\pi D t} \]

where, F, D and t are hardness (kg cm⁻²), compact diameter (cm) and thickness (cm), respectively. Crushing strength of agglomerates was determined using modified Jarosz and Parrot’s mercury load cell method. It was carried out using a 10 mL glass hypodermic syringe. The modifications include removal of the tip of the syringe and the top end of the plunger. The barrel was used as a hollow support and guide tube with close fitting to the plunger. A window was cut at the lower end of the barrel to facilitate placement of the agglomerate on the base plate. The plunger acted as a movable platen. It was set directly on the agglomerate, positioned on the lower platen. Mercury was added to the plunger at a rate of 10 g sec⁻¹ from a separating funnel, from a fixed height. The total weight of mercury plus that of plunger required to break the agglomerate was the crushing strength (g).

For friability studies, 2 g (W₀) of spherical agglomerates (particle size 250-600 μm) was placed in a friabilator and this was subjected to the impact test at 50 rpm for 2 min. After passing this through a sieve having a mesh size 125 μm, the weight (W) of the material which did not pass through the sieve was determined and friability (X) was calculated using equation:

\[ X = \frac{W₀ - W}{W₀} \times 100 \]
Solubility studies: The solubility of piroxicam spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates and adding to screw-capped 50 mL glass vials filled with water. The vials were shaken for 2 h on mechanical shaker. The solution was filtered through Whatmann filter paper No. 1 and the drug concentration was determined spectrophotometrically at 334 nm. Each sample was done in triplicate.

Dissolution studies of agglomerates: The dissolution of piroxicam pure sample, spherical agglomerates and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab. Mumbai). Dissolution medium (750 mL) consisted of (one part of 7.2 Phosphate buffer and four parts of water) was used and 10 mL of dissolution medium was withdrawn at every 10 min interval for 1 h. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 334 nm. Each sample was done in triplicate (Usha et al., 2008).

Determination the physical stability: To determine the physical stability of spherical agglomerates was placed in a climatic chamber of 20°C and 45% Relative Humidity (RH). After 90 days, the %drug release of piroxicam in the spherical agglomerates was determined by dissolution study and compare with freshly prepared spherical agglomerates. Each sample was done in triplicate.

RESULTS AND DISCUSSION
Preparation of spherical agglomerates of piroxicam: A typical spherical crystallization system involved a good solvent, a poor solvent for a drug and a bridging liquid. The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. Piroxicam was dissolved (2.5 g) in excessive of sodium hydroxide (25 mL of 1 N) than was required to neutralize the piroxicam. Crystallization of piroxicam was induced by neutralizing the sodium hydroxide by adding large excess of hydrochloric acid (67 mL of 0.07N). The 8 mL of chloroform was added and stirred till the spherical crystals of piroxicam were obtained.

Reccrystallization of piroxicam: Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence, the mechanical, micromeritic and dissolution properties of spherical crystals were compared with pure sample and recrystallized sample. Recrystallization of piroxicam was carried out using same solvent composition as was used for spherical crystallization (Kulkarni and Dixit, 2010a).

Determination of residual solvents concentration in spherical agglomerates: Residual solvent concentration of chloroform was found to be 2.3 ppm which is well below the tolerated limits i.e., 50 ppm.

Drug content: The yield obtained was in the range of 95±1.54%, with the drug content of 99.36±1.32%.

Optimization of process variables: To optimization piroxicam spherical agglomeration by sodium hydroxide (1 N)/hydrochloric acid (0.07 N)/chloroform system, other process parameters like amount and mode of addition of bridging liquid, stirring speed and time and temperature were considered (Table 1).
Table 1: Effect of variables on formulation of spherical agglomerates of piroxicam

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variable</th>
<th>Observation</th>
</tr>
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<tbody>
<tr>
<td>Conc. of bridging liquid</td>
<td>2%</td>
<td>No agglomeration</td>
</tr>
<tr>
<td>(Chloroform)</td>
<td>8%</td>
<td>Agglomeration</td>
</tr>
<tr>
<td></td>
<td>12.5%</td>
<td>No Agglomeration</td>
</tr>
<tr>
<td>Agitation speed</td>
<td>400±25</td>
<td>Spherical and large</td>
</tr>
<tr>
<td></td>
<td>500±25</td>
<td>Spherical and small</td>
</tr>
<tr>
<td></td>
<td>600±25</td>
<td>Spherical</td>
</tr>
<tr>
<td></td>
<td>700±25</td>
<td>Irregular shape and small</td>
</tr>
<tr>
<td>Agitation time</td>
<td>20 min</td>
<td>Incomplete agglomerates</td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>Spherical agglomerates</td>
</tr>
<tr>
<td>Temperature</td>
<td>5±1°C</td>
<td>No agglomeration</td>
</tr>
<tr>
<td></td>
<td>20°C</td>
<td>Spherical agglomerates</td>
</tr>
<tr>
<td></td>
<td>45±1°C</td>
<td>Very large agglomerates</td>
</tr>
<tr>
<td>Mode of addition of bridging liquid</td>
<td>Whole at a time</td>
<td>Crystals of irregular geometry</td>
</tr>
<tr>
<td></td>
<td>Drop wise</td>
<td>Spherical agglomerates</td>
</tr>
</tbody>
</table>

The average diameter of agglomerated crystals was found to increase with increase in amount of chloroform in the crystallization medium due to enhanced agglomeration of crystals. Agglomerates have excessive bridging liquid on the surface due to coalescence. Size distributions of particles at different concentrations of bridging liquids are shown in Fig. 1.

The movement of droplets within the medium induces circulation inside the droplets. The intensity of this internal circulation depends on the speed. Higher speed (>700 rpm) induces crystal agglomerate destruction. A lower stirring rate (<500 rpm) reduces the possibility of obtaining spherical agglomerates. Size distributions of particles at various degrees of agitation are given in Fig. 2. It is evident from the Fig. 2 that the size of agglomerates very much depended on the degree of agitation. For a constant period of agglomeration, as the speed of agitation increased, the size of agglomerates obtained decreased. This may be due to the fact that as the speed of agitation increases the impact energy for collision of particle increases due to increased turbulence, resulting in agglomerates which are more compact and dense.

The temperature of agglomerating solvents was found to have pronounced effect on the process of spherical agglomeration. Agglomeration and hence formation of crystal agglomerates could not occur when the process was carried out at 5±1°C. It could be due to reduced solubility of drug in agglomerating solvent. This did not affect efficient wetting of drug particles and hence reduced agglomeration. When the temperature of the process was increased to 45±1°C very large agglomerates were produced and the amount of recovery of the drug was reduced. It could be due to increase in solubility of the drug at higher temperature. Optimum agglomeration was achieved at 20±1°C.

Uniform distribution of bridging liquid was achieved when it was added dropwise with continuous stirring of agitator, resulting in formation of spherical agglomerates due to efficient agglomeration. Addition of whole amount of bridging liquid at a time to agglomerating vessel produced spherical agglomerates of irregular geometry. This may be due to localization of bridging liquid and hence its unavailability for efficient agglomeration.

**Differential scanning calorimetry:** The DSC thermograms (Fig. 3) show a sharp endothermic peak for all the piroxicam crystals. This one step melt might be due to only one crystal form
Fig. 1: Effect of amount of bridging liquid on size distribution of spherical agglomerates

Fig. 2: Effect of intensity of agitation on size distribution of spherical agglomerates

Fig. 3: DSC thermograms of piroxicam samples

(Triclinic) of the piroxicam formed during the crystallization process, thus indicating that piroxicam did not undergo any crystal modification. The temperature range of the endothermic peak of all the piroxicam crystals lies in the range of 203 to 199°C. In DSC curve, pure piroxicam had a sharp endothermic peak at 203°C with enthalpy of 174.32 J g⁻¹ that corresponded to the melting point of piroxicam. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated piroxicam was 199.09°C with decreased enthalpy of (156.83 J g⁻¹) indicating decreased crystallinity (Vreec et al., 1991).

**Fourier transform infrared spectroscopy (FTIR):** Infrared spectra of pure piroxicam, recrystallized sample, spherical agglomerates showed characteristic peaks at –NH and –OH stretching which lies at 1385 cm⁻¹, 1635 or 1625 cm⁻¹ (N-H-CO₂ stretching vibration), 1525 cm⁻¹ (secondary -NH₂ stretching), 1440 cm⁻¹ (CH₃ and Ar = c stretching), 1355 cm⁻¹ (sym. -CH₃) and 1155 and 1070 cm⁻¹ or 1050-1070 cm⁻¹ (-SO₂-N⁻) 770 and 740 or 740 cm⁻¹ (Ortho-disubstituted
phenyl) and shown in Fig. 4 (Dix et al., 2004). Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of a solvent of crystallization.

**X-ray analysis:** All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphous of piroxicam was ruled out. However relative intensities of XRD peaks were modified (Fig. 5). This could be attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes (Labrousse et al., 1989).

**Scanning Electron Microscopy (SEM):** Crystals of pure sample are of the smallest size (5-10 μm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (10-15 μm) which had rod like shapes. The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface covered with numerous rod shaped crystals (Fig. 6) (Poovi et al., 2011). Agglomerates obtained were spherical in shape with circularity factor ranging between 1-1.001.

**Micromeritic properties:** The differences in the bulk densities may be related to their markedly different crystal habits, leading to different contact points, frictional and cohesive forces between the crystals Spherical agglomerates exhibited higher packing ability than pure sample. It is due to lower surface area and wider particle size distribution of spherical agglomerates. The smaller crystals might have settled in voids between larger particles. Three measures of flowability were utilized to analyze the flow of particles. Flow rate measurement allowed quick estimation of flow properties. Angle of repose is able to provide gross measurements of the flowability of crystals. Pure sample exhibited higher angle of repose than spherical agglomerates, due to irregular shape and smaller crystal size. The higher flowability of spherical agglomerates was due to perfect sphericity.

![Fig. 4: FT-IR spectra of piroxicam samples](image-url)
Fig. 5: X-ray diffraction spectra of piroxicam samples

Fig. 6: SEM of different sample of piroxicam; (a) pure sample, (b) recrystallized sample, (c) spherical agglomerates and (d) surface of spherical agglomerates

and larger size of the crystals. The compressibility index is a simple and fast method for estimating flow of powder. Powders with compressibility above 40% had poor flow. Flow rates are in agreement with morphology and bulk density, spherical agglomerates with low bulk density exhibits better flow properties (Table 2).

**Mechanical properties:** Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (Fig. 7). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal. The crushing strength of agglomerates was in the range of 90-102 g and was unaffected by the process variables (Kulkarni and Dixit, 2010b).

**Solubility study:** Spherical agglomerates showed increased solubility than the pure sample in water and this could be due to the improve wettability of the spherical agglomerates and result was showed in Table 1.
Fig. 7: Tensile strength of spherical agglomerates and pure sample as a function of compaction pressure

Table 2: Micromeritic properties of pure piroxicam and spherical agglomerates obtained by neutralization method

<table>
<thead>
<tr>
<th>Properties</th>
<th>Pure sample</th>
<th>Recrystallized sample</th>
<th>Spherical agglomerates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size (μm)</td>
<td>6-10</td>
<td>10-15</td>
<td>830</td>
</tr>
<tr>
<td>Flow rate (g sec⁻¹)</td>
<td>No flow</td>
<td>No flow</td>
<td>7.75</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>38.88</td>
<td>36.157</td>
<td>28.72</td>
</tr>
<tr>
<td>Tapped density (g mL⁻¹)</td>
<td>0.925±0.009</td>
<td>0.540±0.04</td>
<td>0.193±0.04</td>
</tr>
<tr>
<td>Bulk density (g mL⁻¹)</td>
<td>0.666±0.0084</td>
<td>0.304±0.08</td>
<td>0.185±0.006</td>
</tr>
<tr>
<td>Carr's index</td>
<td>27.57</td>
<td>27.15</td>
<td>7.41</td>
</tr>
<tr>
<td>Mechanical strength (%)</td>
<td>-</td>
<td>-</td>
<td>0.897±0.65</td>
</tr>
<tr>
<td>Solubility (mg mL⁻¹) in water</td>
<td>0.0084</td>
<td>0.0094</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

[n = SD±3]

Dissolution studies: The dissolution profiles of piroxicam (Fig. 8) exhibited improved dissolution behaviour for spherical agglomerates than pure sample. The reason for this faster dissolution could be linked to the better wettability of the spherical agglomerates. The amount of drug dissolved in 60 min greatly varied for spherical agglomerates (Simchua et al., 2011).

Determination the physical stability: The dissolution behavior of spherical agglomerates must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of spherical agglomerates, the molecular mobility should be as low as possible. However, spherical agglomerates, partially or fully amorphous, are thermodynamically unstable and will have a natural tendency to crystallize, because the crystalline state has a lower energy compared to amorphous material. However, amorphous material can be kinetically stable which implies that the equilibrium state, i.e., crystalline, is not reached within the timeframe of the experiment or shelf life of the product. Therefore, the physical state should be monitored because changes therein are likely to alter the drug release.

The results of the stability study of spherical agglomerates stored at 20°C and 45% relative humidity for 90 days. The influence of spherical agglomerates on the physical stability of piroxicam was investigated. The percent of drug release from spherical agglomerates almost same i.e. (63.28%) after 90 days of storing when compare with the freshly prepared spherical agglomerates i.e., (63.37%). Above result shows that spherical agglomerates of piroxicam was stable after 90 days at 20°C and 45% relative humidity.

Fig. 8: Dissolution profile of piroxicam

CONCLUSION
Spherical crystals of piroxicam were prepared by neutralization crystallization technique. Spherical crystals exhibited decreased crystallinity and improved micromeric properties. Amount of bridging liquid, speed of agitation and duration of agitation affects the mechanical and micromeric properties of spherical crystals. DSC and XRD studies showed that there is no change in the crystal structure of piroxicam during the crystallization process i.e., polymorphism has not occurred. The dissolution of the spherical crystals was improved compared with pure piroxicam sample. Hence this technique can be used for formulation of tablets of piroxicam by direct compression with directly compressible tablet excipients.

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