Research Article

Effect of Additives on the Physicochemical and Drug Release Properties of Pioglitazone Hydrochloride Spherical Agglomerates

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Abstract

Purpose: To prepare and evaluate spherical agglomerates of pioglitazone hydrochloride (PGH) for direct compression with different additives.

Method: Spherical agglomerates of pioglitazone hydrochloride were prepared by emulsion solvent diffusion method with and without additives (polyethylene glycol 6000, polyvinyl pyrrolidone, β cyclodextrin, Eudragit RS100, low acyl gellan gum and xanthan gum) using methanol, chloroform and water as good solvent, bridging liquid and poor solvent respectively. The agglomerates were evaluated for compressibility, solubility and dissolution rate and also by scanning electron microscopy (SEM), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and fourier transforms infrared spectroscopy (FTIR).

Results: The particle size, flowability, compactibility, packability, solubility and dissolution rate of plain agglomerates and agglomerates with additives, except polyvinyl pyrrolidone, were enhanced compared with the original crystals of pioglitazone hydrochloride. This might be attributed to their large size (10 x original PGH crystals), spherical shape, enhanced fragmentation during compaction (yield pressure increased from 22.6 to 29.3 MPa) and reduced elastic recovery of compacts (from 8.1 to 5.5 %) compared to the original drug crystals. XRPD and DSC studies indicate polymorphic transition of PGH in all agglomerates from form II to I during recrystallization; FTIR spectra show that this was not associated with any chemical transition.

Conclusion: The findings indicate that spherical crystallization by emulsion solvent diffusion method to produce agglomerates containing selected additives is a satisfactory approach for the formulation of directly compressed pioglitazone hydrochloride tablets.

Keywords: Spherical crystallization, Agglomerates, Compressibility, Pioglitazone, Emulsion solvent diffusion.

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INTRODUCTION
Direct tabletting is an efficient process involving mixing and compression of powders to save time and cost, compared with granule tabletting [1]. However, it strongly depends on the flowability, compactibility and packability of the drug crystals used; otherwise considerable amounts of excipients are necessary, resulting in oversized tablets. Crystals could be generated by employing any of the available techniques such as sublimation, solvent evaporation, vapor diffusion, thermal treatment, crystallization from melt precipitation and growth in the presence of additives [2]. Fine crystals are preferred to large crystals of poorly soluble pharmaceuticals as they provide greater bioavailability. However, micronization of crystals frequently prevents efficient powder processing due to poor flowability, compactibility and packability [3].

Thus, novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during recrystallization process has been desired. The use of spherical crystallization technique appears to be an efficient alternative for obtaining suitable particles for direct compression [4]. Spherical crystallization is a particle design technique whereby recrystallization and agglomeration are carried out simultaneously in one step and has been successfully utilized for improvement of flowability and compactibility of crystalline drugs [5]. Various methods are reported in the literature for generating spherical agglomerates, including spherical agglomeration (SA), emulsion solvent diffusion (ESD), ammonia diffusion and neutralization [6]. Among these, SA and ESD methods are widely employed [7,8].

Pioglitazone hydrochloride (PGH) is thiazolidinedione oral antidiabetic used in the management of type II diabetes mellitus. It is rapidly absorbed after oral administration; peak plasma concentrations are obtained within two hours [9].

The aim of the present investigation was to study the effect of some additives - polyethylene glycol 6000, polyvinyl pyrrolidone, β cyclodextrin, eudragit RS100, low acyl gellan gum and xanthan gum - on micromeric properties, flowability, compactibility, packability, solubility and drug release of PGH agglomerates prepared using ESD method.

EXPERIMENTAL
Materials
Pioglitazone hydrochloride (PGH) and β cyclodextrin (β-CD) were kindly provided by Alembic Research Centre, Gujarat, India. Low acyl gellan gum (GG) and xanthan gum (XG) were provided by C.P. Kelco Pvt. Ltd. Mumbai (India) free of charge. Eudragit RS 100 (EU), polyethylene glycol 6000 (PEG), polyvinyl pyrrolidone (PVP), methanol and chloroform were purchased from Rajesh Chemicals, Pune, India. All chemical used were of analytical grade.

Preparation of spherical agglomerated PGH crystals
PGH (10 g) was dissolved in a mixture of 60 ml methanol (good solvent) and 40 ml chloroform (bridging liquid). The resultant solution was poured into 500 ml of distilled water (poor solvent) containing 1 %w/v of either PEG, PVP, β-CD, EU, GG or XG, with stirring at 800 rpm for 20 min at 25 ° C. The recrystallized agglomerates obtained were collected by vacuum filtration and dried in an oven at 60 °C for 4 h and stored in a desiccator at room temperature before use. The process was repeated several times for each formulation type to obtain enough for characterization and to assess repeatability.

Determination of yield and drug content
The yield (total dry weight) of the agglomerates was determined by weighing the agglomerates after drying. For determination of drug content, spherical
agglomerates of PGH equivalent to 100 mg of PGH were triturated and dissolved in a solvent system consisting of methanol: water: concentrated hydrochloric acid in a 250:250:1 (ml) ratio. Appropriately diluted samples were filtered through Whatman filter paper no. 41 (pore size 25 µm) and drug content determined spectrophotometrically at 269 nm (model V530, Jasco, Japan).

Micrometric properties of raw crystals and spherical agglomerates

The mean particle size of PGH and its agglomerates was determined by measuring the average diameter of 100 particles (randomly selected) with an optical microscope (model GEM 2121, Gaurav Enterprises, India). Their SEM micrographs were taken (model S120, Cambridge, United Kingdom). Bulk density and tap density was determined as follows. A 50 ml glass cylinder was weighed and filled with 30 g sample. The opening was securely sealed with parafilm. The cylinder was gently inverted once and the powder was carefully leveled without compacting. Bulk volume was determined after one mechanical tap and tap volume was measured after 2000 taps on a tap density tester (model T2, Dolphin, India). Bulk density, tap density, Carr’s index, Hausners ratio and angle of repose by fixed funnel method were determined as in Eqs 1 – 3 [10].

\[
\text{Hausners ratio} = \frac{\text{Tap density} - \text{Bulk density}}{\text{Tap density}} \times 100 \quad \text{(1)}
\]

\[
\text{Angle of repose} = \tan^{-1} \left( \frac{\text{height of pile}}{\text{radius of pile}} \right) \quad \text{(2)}
\]

Solubility study

The solubility of the plain crystals and spherical agglomerates of PGH were determined in both distilled water and pH 2 potassium chloride (KCl) buffer. Excess amount of sample were added to 20 ml of distilled water or KCl buffer, continuously shaken (300 rpm) at 25 ± 0.5 °C for 48 h and sonicated using a sonicator (model T-SONIC, Dolphin, India) for 2 h. The samples were filtered through a 0.45 µm filter and assayed spectrophotometrically for drug content at 269 nm.

Compaction behavior of raw crystals and spherical agglomerates

Heckel study [11] was performed by compressing 500 mg of raw crystals or spherical agglomerates on a hydraulic press (Samrudhi Enterprises, Mumbai, India.) using 13 mm flat-faced punch and die set at pressures of 20, 30, 40, 60, 80, 100 and 120 kN. The thickness, weight and diameter of the compacts were determined. Heckel parameters were determined using Heckel equation (Eq 4). Also, the elastic recovery (ER), thickness of the compact of agglomerates and raw crystal of PGH were determined at a compression pressure 60 kN and at 24 h after releasing the tablet from the die [12].

\[
\ln \left( \frac{1}{1-D} \right) = KP + A \quad \text{…………… (4)}
\]

where \( D \) is the relative density of powder for applied pressure \( P \). The slope of the straight-line portion, \( K \), is the reciprocal of the mean yield pressure (MYP) of the material.

Packability determination

In packability determination, 25 g of the sample was poured slowly and gently into a 25 ml measuring cylinder and tapped for 100, 200, 300, 400, 500, 600, 700, 800, 1100 and 1200 times using a Stampf volumeter. Compactibility and cohesiveness values were calculated using the modified Kawakita and Kuno equations, respectively (Eqs 5 and 6) [13,14].

\[
\left( \frac{n}{Q} \right) = \left( \frac{1}{ab} \right) + \left( \frac{n}{a} \right) \quad \text{…………… (5)}
\]

where, \( C = (V_o - V_f)/V_o, a = (V_e - V_o)/V_o, n = \) number of taps, \( C = \) difference in volume (degree of volume reduction), \( a \) and \( b = \) constant for packability and flowability, respectively, \( V_o = \) initial volume, \( V_f = \) final volume.
volume after \( n^{th} \) tap, and \( V_\infty \) = powder bed volume at equilibrium.

\[
\rho_f - \rho_n = (\rho_f - \rho_o) e^{-kn} \quad \ldots \ldots \ldots \ldots \ldots (6)
\]

The value of \( k \) in Kuno’s equation was determined directly incorporating the density values in Eq 6, where, \( \rho_f \), \( \rho_o \) and \( \rho_n \) are apparent densities at equilibrium, initial state and after \( n^{th} \) tap, respectively.

**Scanning electron microscopy (SEM)**

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

**X-ray powder diffraction (XRD**)  

X-ray powder diffraction of raw crystals and spherical agglomerates were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized \( \text{Cu K}_{\alpha} \) -radiations (1.542 A°) and analyzed between 2 - 60° (2\( \theta \)). 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/20.

**Differential scanning calorimetry (DSC)**

The thermal properties of the raw crystals and spherical agglomerates of PGH were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale while nitrogen was used as the purge gas at a flow rate of 50 ml per min through the DSC cell and 100 ml per min through the cooling unit. The sample (5 – 10 mg) was heated in a hermetically sealed (without perforation) aluminum pans. Heat run was set from 0 to 300 °C at a heating rate of 10 °C/min.

**Fourier transform infrared spectroscopy (FTIR)**

Fourier transform infrared spectroscopy of the raw crystals and spherical agglomerates of PGH was recorded using a model V5300 (Jasco, Japan) FTIR system using potassium bromide (KBr) pellet. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm\(^{-1}\).

**In-vitro dissolution studies**

Dissolution studies on the raw crystals and spherical agglomerates of PGH (equivalent to 100 mg of PGH) were performed using a USP 26 type II dissolution test apparatus (Dolphin™, Mumbai, India) in 900 ml of pH 2 KCl buffer at 37 ± 2°C and 100 rpm stirring. Samples were collected periodically and replaced with equivalent volume of fresh dissolution medium. After filtration through Whatman filter paper 41(pore size: 25 µm), the concentration of PGH was determined spectrophotometrically at 269 nm.

**Statistical analysis**

The results obtained are expressed as mean ± standard deviation (SD) of three replicates. The results were statistically analyzed and significant differences determined by one-way analysis of variance (ANOVA) using “Graph Pad Instat®” Version 3.05 (USA) program. Statistically significant difference was considered at \( p < 0.05 \).

**RESULTS**

**Spherically agglomerated crystals of PGH**

In the absence of a bridging liquid, the system produced agglomerates rich in needle-shaped crystals. At optimized concentration of good solvent and bridging liquid (3:2), the optimum rate was 800 rpm. Formation of lumps and agglomerates of un-
uniform size and shape was observed at lower stirring rates, while high stirring rate destroyed the agglomerates. Yield and drug content of the PGH agglomerates were satisfactory, as shown in Table 1.

### Micrometric properties of agglomerates

The micromeritic properties of the agglomerates are given in Table 1. The particle size of plain agglomerates (i.e., without additive) and agglomerates with additives (except PVP) increased by more than 10 times compared to the original crystals. This may be due to particle aggregation. SEM (figure 1) of drug, plain agglomerates and agglomerates with additives reveals that the agglomerates were spherical and had a smooth surface. The bulk densities of the plain agglomerates and agglomerates with additives (except PVP) was lower than those of the original crystals of PGH. Furthermore, the angle of repose, Carr’s index and Hausner ratio values of the plain agglomerates and agglomerates with additives (except PVP) were lower than those of the original crystals of PGH.

### Compaction behavior of agglomerates

Heckle parameter $MYP$ and $ER$ for the original crystals and agglomerates of PGH are given in Table 2. The elastic recoveries of the compacts of plain agglomerates and agglomerates with PEG, β-CD, EU, GG and XG were smaller than that of the original drug crystals.

### Packability determination

The packability parameters ($a$, $b$ and $k$) obtained from Kawakita and Kuno equations, respectively, are given in Table 3. For plain agglomerates and agglomerates with PEG, β-CD, EU, GG and XG, the value of parameter $a$ in Kawakita equation decreased while parameters $b$ and $k$ in Kawakita and Kuno equations, respectively, increased compared with those of the original crystals of PGH and its agglomerates with PVP.

### Solubility study

The solubility data are given in Table 3. It was observed that solubility of spherical agglomerates was higher than that of the original PGH crystals. Solubility was highest for β-CD agglomerates and lower for PVP agglomerates.

### X-ray powder diffraction (XRPD)

PGH has at least two polymorphic forms, namely, forms I and II. Diagnostic peaks for form I are at $2\theta$ = 8.7, 12.7, 18.8, 20, 20.1, 22.7, 26.6, 28.3 and for form II, they are at $2\theta$ = 9.2, 10.4, 15.2, 16.4, 18.6, 21.4 [15]. XRPD diffractograms show in Figure 2(I) indicate that PGH crystals were form II but changed to form I in the agglomerates.

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Table 1: Micrometric properties of original crystals and agglomerates of PGH

<table>
<thead>
<tr>
<th>PGH type</th>
<th>Yield (%) (n=3)</th>
<th>DC (%) (n=3)</th>
<th>Mean diameter (µm) n=100</th>
<th>Angle of repose (°) (n=3)</th>
<th>Bulk density (g/cc) (n=3)</th>
<th>Carr’s index (%) (n=3)</th>
<th>Hausner ratio (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original crystals</td>
<td>-</td>
<td>-</td>
<td>16.7±1.1</td>
<td>52.2±0.7</td>
<td>0.32±0.01</td>
<td>32.3±0.5</td>
<td>1.42±0.04</td>
</tr>
<tr>
<td>Plain agglomerate</td>
<td>96±2</td>
<td>92±2</td>
<td>162.3±1.1</td>
<td>23.1±0.6</td>
<td>0.21±0.01</td>
<td>15.0±0.4</td>
<td>1.18±0.05</td>
</tr>
<tr>
<td>Agglomerate with PEG</td>
<td>95±1</td>
<td>94±1</td>
<td>151.5±0.8</td>
<td>22.2±0.7</td>
<td>0.28±0.01</td>
<td>14.1±0.6</td>
<td>1.16±0.04</td>
</tr>
<tr>
<td>Agglomerate with β-CD</td>
<td>97±1</td>
<td>91±3</td>
<td>158.7±1.2</td>
<td>23.2±0.2</td>
<td>0.27±0.01</td>
<td>14.1±0.7</td>
<td>1.16±0.05</td>
</tr>
<tr>
<td>Agglomerate with EU</td>
<td>95±2</td>
<td>92±2</td>
<td>146.5±0.7</td>
<td>24.1±0.3</td>
<td>0.27±0.00</td>
<td>15.0±0.5</td>
<td>1.17±0.06</td>
</tr>
<tr>
<td>Agglomerate with GG</td>
<td>94±2</td>
<td>93±1</td>
<td>149.5±0.8</td>
<td>26.1±1.1</td>
<td>0.28±0.01</td>
<td>14.3±0.7</td>
<td>1.16±0.09</td>
</tr>
<tr>
<td>Agglomerate with XG</td>
<td>97±1</td>
<td>91±2</td>
<td>152.5±0.5</td>
<td>21.2±0.9</td>
<td>0.27±0.01</td>
<td>18.7±1.1</td>
<td>1.23±0.03</td>
</tr>
<tr>
<td>Agglomerate with PVP</td>
<td>92±3</td>
<td>90±2</td>
<td>18.4±1.0</td>
<td>39.2±0.4</td>
<td>0.33±0.00</td>
<td>31.2±0.5</td>
<td>1.45±0.03</td>
</tr>
</tbody>
</table>

Differential scanning calorimetry (DSC)

PGH crystals showed a melting endotherm at 192.6 °C with heat of fusion -99.24 J/g, as shown in Figure 2(II).

Table 2: Heckel-derived parameters, namely, MYP (mean yield pressure) and ER (elastic recovery) of PGH crystals and agglomerates (n = 3)

<table>
<thead>
<tr>
<th>PGH type</th>
<th>MYP (MPa)</th>
<th>% ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystals</td>
<td>22.5± 2.4</td>
<td>8.1 ± 1.2</td>
</tr>
<tr>
<td>Agglomerate (plain)</td>
<td>27.4± 1.8 **</td>
<td>4.8 ± 0.4 ***</td>
</tr>
<tr>
<td>Agglomerate with PEG</td>
<td>25.3± 1.6 **</td>
<td>5.1 ± 0.6 ***</td>
</tr>
<tr>
<td>Agglomerate with β-CD</td>
<td>28.3± 2.3 **</td>
<td>5.0 ± 0.5 ***</td>
</tr>
<tr>
<td>Agglomerate with EU</td>
<td>26.3± 1.5 **</td>
<td>5.8 ± 0.7 ***</td>
</tr>
<tr>
<td>Agglomerate with GG</td>
<td>29.3± 1.2 **</td>
<td>6.1 ± 0.8 ***</td>
</tr>
<tr>
<td>Agglomerate with XG</td>
<td>26.3± 1.7 **</td>
<td>5.5 ± 0.4 ***</td>
</tr>
<tr>
<td>Agglomerates with PVP</td>
<td>21.3± 2.9 *</td>
<td>7.8 ± 0.8 *</td>
</tr>
</tbody>
</table>

*** p < 0.001; ** p < 0.01; * p < 0.05, compared with PGH crystals. Note: PEG = polyethylene glycol 6000, β-CD = β-cyclodextrin, EU = Eudragit RS 100, GG = low acyl gellan gum, XG = xanthan gum, PVP = polyvinyl pyrrolidone

Fourier transforms infrared spectroscopy (FTIR)

Fig 2(III) shows that the FTIR spectrum of PGH original crystals displayed absorption bands at 3358, 2928, 2854, 1741, 1705, 1610, 1516, 1460, 1383, 1333, 1254, 1180, 1159, 1040, 1012, 824, 719, 658, 598, 563, 542, 521 cm⁻¹. The characteristic absorption peaks of PGH are 3358 for N-H stretching, 2928 and 2855 for C-H stretching in CH₂ group, 1742 and 1705 for asymmetric C=O stretching, 1610 and 1516 for C=C stretching, 1460 for CH₂ deformation, 1383 for asymmetric CH₃ deformation, 1333 mixed vibration, 1254 for C-H bending, 1181 for C-O stretching, 1159 for CH₂ wagging, 1044 for C-H bending, 1017 for CH₃ scissoring, 720 for CH₂ rocking, 658 and 598 for ring deformation, 563 for C=O bending, 542 for N-H bending, and 521 for C-C bending in benzene ring. Thus PGH crystals and spheri-
Table 3: Kawakita constants $a \times 10^{-2}$, $b \times 10^{-4}$ and Kuno’s constant $k \times 10^{-4}$ and solubility data for original crystals and agglomerates of PGH. (n=3)

<table>
<thead>
<tr>
<th>PGH type</th>
<th>$a$</th>
<th>$b$</th>
<th>$k$</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Water</td>
</tr>
<tr>
<td>Crystals</td>
<td>43±0.06</td>
<td>30.4±0.005</td>
<td>25.8±0.001</td>
<td>30±1.2; 109±2.3</td>
</tr>
<tr>
<td>Agglomerate (plain)</td>
<td>27.4±0.05</td>
<td>25.5±0.003</td>
<td>10.8±0.006</td>
<td>76±1.6 ***; 227±3.1 ***</td>
</tr>
<tr>
<td>Agglomerate with PEG</td>
<td>28.8±0.06</td>
<td>11.8±0.004</td>
<td>10.2±0.004</td>
<td>82±2.1 ***; 268±2.1 ***</td>
</tr>
<tr>
<td>Agglomerate with β-CD</td>
<td>28.8±0.03</td>
<td>10.4±0.006</td>
<td>10.5±0.006</td>
<td>98±1.8 ***; 408±4.3 ***</td>
</tr>
<tr>
<td>Agglomerate with EU</td>
<td>27.8±0.02</td>
<td>21.±0.003</td>
<td>11.0±0.003</td>
<td>78±1.1 ***; 248±3.2 ***</td>
</tr>
<tr>
<td>Agglomerate with GG</td>
<td>28.1±0.04</td>
<td>19.5±0.006</td>
<td>10.7±0.007</td>
<td>68±2.2 ***; 238±2.6 ***</td>
</tr>
<tr>
<td>Agglomerate with XG</td>
<td>29.6±0.03</td>
<td>31.6±0.009</td>
<td>11.8±0.008</td>
<td>71±1.9 ***; 255±2.9 ***</td>
</tr>
<tr>
<td>Agglomerate with PVP</td>
<td>43.5±0.07</td>
<td>31.3±0.006</td>
<td>26.2±0.003</td>
<td>49±1.4 **; 136±1.6 **</td>
</tr>
</tbody>
</table>

*** p < 0.001; ** p < 0.01; * p < 0.05, compared with PGH crystals. Note: PEG = polyethylene glycol 6000, β-CD = β-cyclodextrin, EU = Eudragit RS 100, GG = low acyl gellan gum, XG = xanthan gum, PVP = polyvinyl pyrrolidone

In-vitro drug release

As shown in Figure 3 for PGH crystals, approximately 67% of the drug was released in 30 min while for the agglomerates, drug release within the same period was > 95% except for the agglomerate with PVP which exhibited 85% drug release. Increase in drug release was in the order: β-CD > PEG > EU > XG > GG > plain > PVP > raw crystals.

DISCUSSION

PGH agglomerates

When the solution of drug in good solvent and bridging liquid was poured into the poor solvent, quasi-emulsion droplets of the drug solution were produced initially. Subsequently, crystallization of the drug occurred at the outer surface of the droplet. The spherically agglomerated crystals were produced simultaneously after complete crystallization and hence the whole process is known as emulsion solvent diffusion [6]. Under stirring, the agglomerates were spheronized and compacted.
Figure 3: Drug release profile of, PGH crystals (∆), plain agglomerates (●), agglomerates prepared with polyethylene glycol 6000 (▲), agglomerates prepared with β-cyclodextrin (○), agglomerates prepared with Eudragit RS 100 (◊), agglomerates prepared with xanthan gum (●), agglomerates prepared with low acyl gellan gum (■), and agglomerates prepared with polyvinyl pyrrolidone (□).

Micrometric properties

Reduction in the bulk densities of the agglomerates indicates the greater porosity within the agglomerates [17]. PVP most effectively decreased the mean diameter of the agglomerates probably due to its adsorption on the surface of the crystals thus hindering crystal aggregation. The angle of repose, Carr’s index and Hausners ratio values of the agglomerate with PVP indicate poor flowability. In case of agglomerates with PEG, β-CD, EU, GG and XG average diameter was higher than for the original crystals but lower than for plain agglomerates. These findings suggest that these additives were poorly adsorbed at the surface which would reduce interfacial tension between bridging liquid and crystals, with a consequent decrease in the adhesive force acting to agglomerate the crystals [18].

Compaction behavior

The compressibility of a material is its ability to reduce in volume as a result of an applied pressure [10]. $D_b$ value represents the particle rearrangement phase in early compression stage and tends to indicate the extent of particle fragmentation. Higher $D_b$ values indicated that the agglomerates were highly fractured during the early stage of compression although fragmentation is followed by plastic deformation. The results were well supported by higher yield pressure (MYP) values. The improved compactibility of agglomerates might be attributed to a characteristic structure responsible for the large relative volume changes during the early stage of the compression process due to their fragmentation. Elastic recovery studies have suggested that agglomerated crystals are easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression [19]. The lower $D_b$ value of the agglomerate with PVP compared to the other agglomerates may be attributed to its small particle size.

Packability

The packability of plain agglomerates and agglomerates with PEG and β-CD were improved as a results of agglomeration, thus making them suitable for direct compression tabletting. During tabletting, these agglomerates should flow smoothly from the hopper into die cavity to attain the uniformity in weight necessary in direct tabletting. The improvement in packability and flowability is attributable to size enlargement and the spherical shape of the agglomerates [17].

Solubility and in-vitro drug release

Increase in solubility and dissolution rate of agglomerates of PGH may be attributed to increase in wettability and porosity brought about by the additives. The contrary results for PVP agglomerates is probably due to the

possibility that hardly any agglomeration occurred when PVP was used as an additive.

**X-ray powder diffraction (XRPD)**

XRPD of the original crystals of PGH indicate form II and those of the agglomerates corresponded to form I [15], thus demonstrating that during crystallization of PGH, there was polymorphic transition of PGH from form II to form I. The evidence is the absence of peaks at 8.7, 20, 22.7 and 26.6 in the agglomerates of PGH.

**Differential scanning calorimetry (DSC):**

DSC is generally combined with XRPD to determine polymorphic composition of pharmaceutical powders when polymorphs present different melting points. The DSC study confirms that the original PGH crystals is form II and it was changed to form I during agglomeration and recrystallization [15].

**Fourier transforms Infrared spectroscopy**

The FTIR study clarifies that the altered XRPD spectra and DSC thermograms of the drug and its agglomerates were not associated with any changes at the molecular level [16]. It revealed that no chemical transition occurred during recrystallization of PGH.

**CONCLUSION**

Spherical agglomerates of PGH were successfully prepared by emulsion solvent diffusion method. Flowability, compactibility, packability, solubility and dissolution were greatly improved for all the agglomerate types of PGH, except with PVP. During agglomeration polymorphic transition occurred but this was not associated with changes at molecular level. Spherical crystallization of PGH with selective additives is a satisfactory method for direct tabletting of PGH. However, scale-up would be required to determine if the method can be used for large-scale production of suitable PGH agglomerates.

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