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The impacts of method selectivity and binders on the properties of carbamazepine granules and their applications: A Case Study

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ABSTRACT:

Background: Carbamazepine (CBZ) is a BCS II class drug, having many challenges in solubility, flowability, and compactibility. The study focused on the improvement of solubility, flow behavior, and drug release of carbamazepine.

Methods: Low shear granulation (LSG), extrusion spheronization (ES), high shear granulation (HSG), fluid bed granulation (FBG), and hot melt granulation (HMG) methods were employed to prepare CBZ granules. Polyvinylpyrrolidone (PVP) K29/32, PVP K90, and Hydroxypropyl methylcellulose (HPMC) E5 were used as a binder. The drug to binder ratio was maintained in the proportion of 95:5. The nature of granules was analyzed by using X-ray Diffraction and Differential Scanning Calorimetry techniques. A powder flow tester was utilized to study the flow characteristics of the granules.

Results: The HMG has successfully converted the crystalline structure of CBZ granules into an amorphous form. Dispersive and distributive mixing in the HMG has achieved better solid dispersion and fast drug release. The ES technique has reported the incompressible nature of the granules. PVP K90 and HPMC E5 were superior binders for imparting strength to the CBZ granules than PVP K29/32. The FBG has exhibited the free-flowing nature of granules due to their uniform and spherical shape.

Conclusion: The HMG and FBG were the most effective methods that have remarkably improved drug release, flow properties, and compactibility of CBZ granules.

Keywords: Granulation, Carbamazepine, Binder, Fluid, Melt.

Introduction

Designing and optimizing solid dosage forms requires a fundamental understanding of process variables and excipient properties to develop the final product with the desired flow properties such as good powder flow, good compressibility, better compatibility, and stability. Most active pharmaceutical ingredients possess cohesion and poor flow properties due to their smaller particle size and non-spherical shape. Granulation plays a crucial role in overcoming such limitations. Granulation is the agglomeration of smaller particles into a larger entity\(^1\). Granulation helps prevent particle segregation from mixtures, improvises the flow properties, increases the compaction capacity,\(^2\), and optimizes the spherical shape to reduce the frictional force between granules or particles. The granulation process involves three different steps: wetting and nucleation, coalescence or consolidation of growth, and
attrition or breakage. Various granulation methods have been reported in the literature that classifies granulation types and subtypes.\textsuperscript{2,3}

A comparative granulation study is the most suitable platform to screen granulation techniques to select, develop, and optimize formulation with desired flow properties. Present work encloses LSG, ES, HSG, FBG, and HMG. A lot of literature has been reported on such practices with various drugs and excipients. LSG and HSG with varying excipient levels, the type of mixture, and the compression pressure have been well covered.\textsuperscript{4} A comparative study of high-dose, low-water soluble, low-density, micronized drugs was conducted by fluid bed processing and HSG. The study was focused on achieving comparable results in terms of dissolution rate between these two techniques.\textsuperscript{5} The importance of Moisture-activated dry granulation and applications in solid dosage form have been reported in the literature.\textsuperscript{6} Comparing the moist granulation with the direct compression has concluded that moist granulation yields a larger particle size than direct compression.\textsuperscript{7}

The use of sematilide hydrochloride formulation with planetary mixer, roller compaction, direct compression, moisture-activated dry granulation, traditional wet granulation has been enclosed in the literature.\textsuperscript{8} Tablets produced by the moisture-assisted dry granulation have confirmed a higher level of consistency than those produced by wet and dry granulation processes. Other tablet properties, such as friability and dissolution, were similar to wet granulation, dry granulation, direct compression, and roller compactor. One of the literature deals with the advantages of roller compactor over slugging to achieve higher production capacity, more control over operating parameters, and optimized residence time for the minimum need for powder lubricant.\textsuperscript{9} The HMG was used to prepare granules using low melting point excipients with no binding solution or liquid. The study has explained several of the advantages of HMG over conventional granulation methods.\textsuperscript{10} A comparison of the fluidized bed processor with the high shear mixer has been made. The fluidized bed technique has obtained more prominent granules with better flowability and less friability than granules prepared by a high shear mixer.\textsuperscript{11} The significance of excipient wettability in tableting has been explained by moisture-assisted dry granulation and HSG. The study suggests wettability of powder plays a vital role in the disintegration of tablets.\textsuperscript{12} Comparison of HSG and FBG by continuous ring layer wet granulation has been made. Ring layer wet granulation was easier to control linear responses encountered than the high shear and fluid bed granulation process.\textsuperscript{13}
This work comprises two polymers as Polyvinylpyrrolidone (PVP) and Hydroxypropyl methylcellulose (HPMC). PVP is a non-toxic, hydrophilic, off-white powder. It is mainly used as a coating and binding agent in solid dosage forms.\textsuperscript{14,15} Two different grades of PVP, i.e., PVPK29/32 and PVP K90, have been used in this study. The molecular weight of PVPK29/32 and PVP K90 are 58000 and 1300000, respectively. Both of these polymers possess a wide operating range, and their glass transition temperatures lie in between 160-175°C. HPMC is slightly white to off-white powder. It is a cellulose ether polymer that radially gets dissolved in water by swelling and subsequent hydration. It builds viscosity with mild agitation, and viscosity is directly proportional to its molecular weight. HPMC E5 grade having molecular weight 28700 has been used in this work.\textsuperscript{16} It is highly hygroscopic; hence the end product is stored in a sealed container.

In the present work, BCS II drug class carbamazepine (CBZ) has been selected as a model drug because it has many challenges in achieving good flow properties and acceptable compressibility.\textsuperscript{17} Developing the end product of CBZ with desired flow properties requires many trials to select and design the granulation technique. Simultaneously, each practice utilizes research costs and time that increase the burden of a research scientist or formulator. Therefore, this research aims to study LSG, ES, HSG, FBG, and HMG with CBZ in a comparative way to reduce trial costs and time.

**Materials and methods**

**Materials**

Carbamazepine was collected from Bajaj Healthcare, Aurangabad. Polyvinylpyrrolidone binders (PVP K 29/32 and PVP K90) have been collected from Ashland, Pvt. Ltd. Mumbai, India. Hydroxymethyl propyl cellulose (HPMC E5) was received from Dow chemicals, Mumbai. S.B. Panchal Company, Mumbai, supplied the high shear granulator. Aeroperl 300 pharma was provided as a gift sample by Evonik Degussa India Pvt Ltd, Mumbai, India. Magnesium stearate was purchased from Nitika Pharmaceutical Specialties Pvt. Ltd., INDIA. Monohydrate lactose (Meggle, Germany) and polyethylene glycol (PEG) were supplied by Signet Excipients Pvt. Ltd., Mumbai.

**Methods**

**Preparation of blend**

Carbamazepine and binders were sifted through 16 mesh separately to confirm no lumps inside of the material. Then, the drug and binders were mixed individually (PVP K 29/32, PVP K90, and HPMC E5) in a ratio of 95:5 in three different batches. V cone blender was
utilized to blend the mixture for 10 minutes at 20 rpm. Subsequently, the blend was subjected to mentioned granulation methods.

Low shear granulation (LSG)
Hobart mixture was employed to blend 100 gm of the batch with a sufficient water amount. Blending was continued till a desirable consistency was reached. The wet mass was then passed through 16 mesh forming granules. The granules were air-dried in the oven for one hour at a temperature of 40°C.

Extrusion spheronization (ES)
About 100 gm of the blend was converted into a wet mass with the addition of purified water. The wet mass was extruded by an extruder having a standard screen with an opening of 0.8 mm in diameter and a screw speed of 30 rpm. Extrudes were then transferred to the spheronizing bowl equipped with a 1 mm crosshatch plate and processed at a rotation speed of 700 rpm for 2-3 min. Finally, the granules were air-dried at 40°C for one hour in a hot air dryer.

High shear granulation (HSG)
100 gm of the blend was added to the high shear granulator and operated at 500 rpm for 2-3 minutes. The water was sprayed from the top during the process for 20 sec. The collected granules were dried in a hot air dryer at 40°C for one hour.

Fluid bed granulation (FBG)
The batch of 300 gms was granulated by using Ganson fluid bed granulator (Ganson, Pvt. Ltd. Thane, Mumbai). The blend was homogenized for five minutes with one bar under atomizing pressure. The process was maintained at an inlet temperature of 60°C and bed temperature between 40-80°C. A top nozzle spray system (0.8 mm) was employed to deliver water at a rate of 2-4 gm / min. The obtained granules were dried, and moisture content was noted.

Hot melt granulation (HMG)
The mixture was blended with polyethylene glycol (5% - 7% w/w) as a plasticizing agent and was added to the hopper. The HME was operated at a controlled screw speed of 50 revolutions per minute at 60 -70°C. The granules were collected and cooled.

Physical mixture

Characterization of granules
Particle size distribution study
The particle size distribution study was conducted with an electronic sieve shaker. Standard mesh sieves numbers 18, 25, 40, 60, 80, 100, and 120 were arranged in ascending order from top to bottom. The 100 gms sample was placed on top of the sieve and mechanically shaken for 10 minutes. The weight of the sample retained on each screen was recorded.

**Friability of granules**

The friability of samples was evaluated using a drum-type friabilitor (Abrasion drum-EF 2W Electrolab India Pvt. Ltd.). Granules or tablets were dropped from a six-inch height in a plastic chamber at 25 rpm for 4 min. The final weight of the sample was noted. Equation (1) was used to calculate the friability of the sample,

\[
\%\text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]  

(1)

**Growth of granules**

The integrated light scattering Mastersizer 2000 MU (Malvern Instruments Ltd., Malvern, UK) was used to study particle size. The values were presented in \(d_{10}, d_{50}, \) and \(d_{90}.\) 10, 50, and 90 indicate a median particle diameter.

**Flow properties of granules**

**a. Bulk density \((D_B)\)**

25-30 gms of the sample was taken into 50 ml of measuring cylinder, and the sample volume was noted. Equation (2) was used to calculate bulk density in triplicates,

\[
D_B = \frac{M}{V}
\]  

(2)

Where,

\(M = \) mass of the sample

\(V = \) Pour volume of the sample

**b. Tapped density \((D_T)\)**

The sample was poured into the measuring cylinder mounted on the Lab India density tester. The initial volume and final volume after tapping were noted. About 300, 500, and 1250 taps were conducted for each sample. Tap density was calculated by equation (3),

\[
D_T = \frac{M}{V_T}
\]  

(3)

Where,

\(M = \) mass of the sample

\(V_T = \) volume of the sample after tapping

**c. Measurement of carr index**

Carr index is the ability of the powder to flow. Carr index was evaluated by using bulk density and tap density values of the sample. Equation 4 defines the carr index.\(^{18,}\)
\[
\frac{(D_T - D_B)}{D_T} \tag{4}
\]
Where \(D_T\) is tapped density, and \(D_B\) is bulk density.

d. Housner ratio

Housner ratio is the ratio of tap density to bulk density. It is the number that indicates the flowability of powder or granules. It is defined by the equation (5)

\[
\frac{(D_T / D_B)} \tag{5}
\]

The moisture content of granules

The moisture content was evaluated by using The Citizen MB-50 humidity balance. A sample was heated by placing 4-5 grams of sample in a sample holder for 0-5 min in triplicates.

Scanning Electron Microscope

Scanning electron microscopy (SEM), XL 30 Model, JEOL 5400, Japan; used to observe the nature and shape of granules.

Powder X-ray Diffraction

The Crystalline nature of granules was analyzed by a MiniFlex II desktop powder X-ray diffractometer (Rigaku Corporation, Japan) with Ni-filtered Cu Kβ-radiation. The sample was placed on a glass top holder with a width of 0.03° having a depression of 0.2 mm. Consolidation was applied, and scanning was carried out continuously within the angular range 3–40°, 20 with a scan speed of 2.0° min⁻¹.

DSC analysis

The granules were characterized by Shimadzu DSC TA 60 with a built-in computerized thermal data station. The sample was taken into the aluminum pan for heating. The pan temperature was gradually increased from 30 to 300 °C at a rate of 10 °C / min. An empty aluminum pan was considered a reference sample. The flow of nitrogen flow of the system was maintained at 20 ml per minute.

Powder flow tester (PFT)

The sample weight was recorded in the PFT software program by employing a sample into 230 cc trough. The wall function lid carried the bulk density test, and Van lid was used to assess the flow function test. The axial speed of the trough was maintained at 1 mm/second with a torsional rate of 1 rpm during the evaluation. Preinstalled software, powder flow pro V1.2, was handled to run the standard flow function program. The flow properties of granules were evaluated over the five geometric progressive major principal consolidation stresses (0.007, 0.293, 0.589, 1.187, 2.392, and 4.827 kPa). Each sample was consolidated at
mentioned compacting load. Major principal consolidating stress, unconfined failure strength, density, and effective friction angle were recorded by preinstalled software.

Processing of tablets and evaluation

Tablets preparation

Cadman Rotary tablet press machine was utilized for tablet processing. Concave punches with a diameter of 9/18 were used to prepare 400 mg tablets. Tablets were compressed with increasing levels of compression forces such as 2.5 kN, 5.0 kN, 7.5 kN, 10.0 kN, 15.0 kN, and 25 rpm. Content uniformity, weight variation, thickness and hardness of the tablets were evaluated for ten representative samples for each batch.

Tablet hardness and thickness evaluation

Electrolab hardness tester model: EH01 was used to evaluate the hardness of the tablets (kg/cm square). The thickness of the tablets was verified by Vernier caliper (Electrolab Pvt Ltd.) by considering ten tablets. Tensile strength was calculated by equation (6)

\[
\text{Tensile strength} = \frac{2F}{\pi D T}
\]

(6)

Where,

F is the hardness, D is the diameter, and T is the tablet thickness.

Tablet weight variation

Average tablets weight and weight variation were calculated for ten tablets from each sample. The variability was defined as % RSD for ten tablets.

Content uniformity

Tablets were chosen from the beginning, middle, and end of a compression run. A UV spectrophotometer was sued for the assay of tablets. Variability (%RSD) of tablets in the assay was calculated as the average assay percentage.

In vitro drug dissolution study

USP II Dissolution apparatus (Electrolab Pvt Ltd.) was utilized for the In vitro drug dissolution study. The dissolution tester was operated at 50 rpm, and 37 ± 0.5 °C. 5 ml samples were withdrawn at the sampling time point.

Stability studies

As per ICH guidelines (40 ± 2 °C and 75 ± 5% RH), accelerated stability studies were carried out for six months in a stability chamber (Thermolab, Mumbai, India). Vials with bromobutyl rubber plugs sealed with aluminum caps were used to preserve the samples. Aliquots were collected at 30, 60, 90, and 180 days to calculate drug content.

Results and discussion
Characterization of granules

Particle size distribution

Figure 1. Particle size analysis of granulation techniques (a) Pure CBZ (b) LSG (C) ES, Mean values ± SD (n=3)
Figure 2. Particle size analysis of granulation techniques (a) HSG (b) FBG (C) HMG, Mean values ± SD (n=3)

The particle size distribution data has been represented in Figures 1. and 2. About 60 % fraction of pure CBZ was found between 100-75 µm. A narrow range of particle size distribution and more fines were observed in granules made from LSG and HSG. Granules prepared from ES reported a bigger size of granules in the range 707 to 420 µm. FBG
granules exhibited uniform size distribution. HMG has remarkably notified all sizes of granules with a wide range of size distribution. All used granulation techniques have shown desirable output with no big lump or wall adhesion during the granulation process.

Table 1. The particle size distribution of granules granulation techniques

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Method</th>
<th>d_{10}</th>
<th>d_{50}</th>
<th>d_{90}</th>
<th>f (d_{90}/d_{10})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure CBZ</td>
<td>-</td>
<td>5.32</td>
<td>69.03</td>
<td>82.2</td>
<td>1.36</td>
</tr>
<tr>
<td>CBZ+PVPK29/32(5%)</td>
<td>LSG</td>
<td>98.2</td>
<td>141.2</td>
<td>192.6</td>
<td>1.96</td>
</tr>
<tr>
<td>CBZ+PVPK90(5%)</td>
<td>LSG</td>
<td>115.1</td>
<td>159.4</td>
<td>239.6</td>
<td>2.08</td>
</tr>
<tr>
<td>CBZ+HPMCE5(5%)</td>
<td>LSG</td>
<td>107.3</td>
<td>137.9</td>
<td>220.4</td>
<td>2.05</td>
</tr>
<tr>
<td>CBZ+PVPK29/32(5%)</td>
<td>ES</td>
<td>121.56</td>
<td>169.90</td>
<td>291.4</td>
<td>2.39</td>
</tr>
<tr>
<td>CBZ+PVPK90(5%)</td>
<td>ES</td>
<td>148.12</td>
<td>193.7</td>
<td>394.6</td>
<td>2.71</td>
</tr>
<tr>
<td>CBZ+HPMCE5(5%)</td>
<td>ES</td>
<td>129.34</td>
<td>184.7</td>
<td>353.7</td>
<td>2.73</td>
</tr>
<tr>
<td>CBZ+PVPK29/32(5%)</td>
<td>HSG</td>
<td>107.3</td>
<td>158.8</td>
<td>228.9</td>
<td>2.13</td>
</tr>
<tr>
<td>CBZ+PVPK90(5%)</td>
<td>HSG</td>
<td>135.7</td>
<td>177.1</td>
<td>255.9</td>
<td>1.88</td>
</tr>
<tr>
<td>CBZ+HPMCE5(5%)</td>
<td>HSG</td>
<td>128.3</td>
<td>159.6</td>
<td>248.3</td>
<td>1.93</td>
</tr>
<tr>
<td>CBZ+PVPK29/32(5%)</td>
<td>FBG</td>
<td>118.55</td>
<td>151.6</td>
<td>252.6</td>
<td>2.13</td>
</tr>
<tr>
<td>CBZ+PVPK90(5%)</td>
<td>FBG</td>
<td>142.51</td>
<td>179.9</td>
<td>377.9</td>
<td>2.65</td>
</tr>
<tr>
<td>CBZ+HPMCE5(5%)</td>
<td>FBG</td>
<td>124.88</td>
<td>161.5</td>
<td>341.8</td>
<td>2.73</td>
</tr>
<tr>
<td>CBZ+PVPK29/32(5%)</td>
<td>HMG</td>
<td>104.2</td>
<td>151.3</td>
<td>204.9</td>
<td>1.96</td>
</tr>
<tr>
<td>CBZ+PVPK90(5%)</td>
<td>HMG</td>
<td>121.4</td>
<td>163.5</td>
<td>268.3</td>
<td>2.21</td>
</tr>
<tr>
<td>CBZ+HPMCE5(5%)</td>
<td>HMG</td>
<td>117.34</td>
<td>152.66</td>
<td>243.5</td>
<td>2.07</td>
</tr>
</tbody>
</table>

Table 1 has shown particle size distribution by Marven. Factor (f) represents particle size distribution width, which is a ratio of d_{90}/d_{10}. Compared to Pure CBZ, all used granulation processes have exhibited higher density and particle enlargement. The larger size of granules growth has been confirmed by the ES, followed by FBG. Granules prepared from ES batch CBZ+HPMCE5(5%) have recorded the largest granule, and LSG batch CBZ+PVPK29/32(5%) have recorded relatively smaller granules.

*Strength of the granules*
The strength of granules is implied by friability in Figure 3. The given data has indicated percent friability of CBZ granules prepared from PVP K29/32 is higher than PVP 90 and HPMC E5. The higher molecular weight of PVP K90 imparts higher viscosity to the binding.
solution that has increased the strength of the granules. In HPMC E5, intermolecular hydrogen binding provides more strength and prevents the rupture of granules. Hence, PVP K90 and HPMC E5 would be better as binders than PVP K29/32. ES granules have confirmed relatively minimum percent friability than used granulation techniques. During extrusion spheronization, wet mass was forced through the die of the extruder. The wall pressure of the barrel has induced particle rearrangement. Voids between larger particles have got filled with smaller granules efficiently. As a result, the particle becomes denser and resists to rupture. ES and FBG granules exhibited less friability and better strength to avoid wear and tear of the material during transportation.

Flow properties of granules

The flow properties of the granules have been represented in Table 2. The flowability can be described from the Carr index or Housner ratio. Their values are considered as per USP to interpret the flow of granules. Though particle shape, size, nature, inter-particular friction, and density affect flowability, density has played a significant role here. Plain CBZ possesses a very low density that adds fluffiness to CBZ and reduces flowability. Fluid bed granules and extrusion spheronized granules have shown excellent granules flow due to their dense

<table>
<thead>
<tr>
<th>Method</th>
<th>Batch</th>
<th>(D_h)</th>
<th>(D_t)</th>
<th>Houser ratio</th>
<th>Carr Index</th>
<th>Mc (%)</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSG</td>
<td>CBZ+PVPK29/32(5%)</td>
<td>25.2</td>
<td>34.1±0.8</td>
<td>1.35±0.03</td>
<td>26.09±1.76</td>
<td>1.68</td>
<td>Poor</td>
</tr>
<tr>
<td>LSG</td>
<td>CBZ+ PVPK90(5%)</td>
<td>25.4</td>
<td>34.5±0.8</td>
<td>1.35±0.03</td>
<td>26.37±1.73</td>
<td>1.88</td>
<td>Poor</td>
</tr>
<tr>
<td>LSG</td>
<td>CBZ+HPMCE5(5%)</td>
<td>25.1</td>
<td>35.6±1.2</td>
<td>1.41±0.04</td>
<td>29.49±2.38</td>
<td>1.74</td>
<td>Poor</td>
</tr>
<tr>
<td>ES</td>
<td>CBZ+PVPK29/32(5%)</td>
<td>25.3</td>
<td>27.2±0.8</td>
<td>1.09±0.03</td>
<td>8.33±2.70</td>
<td>2.43</td>
<td>Very good</td>
</tr>
<tr>
<td>ES</td>
<td>CBZ+ PVPK90(5%)</td>
<td>25.1</td>
<td>27.4±0.7</td>
<td>1.09±0.02</td>
<td>8.39±2.32</td>
<td>2.51</td>
<td>Very good</td>
</tr>
<tr>
<td>ES</td>
<td>CBZ+HPMCE5(5%)</td>
<td>25.2</td>
<td>27.4±0.9</td>
<td>1.08±0.03</td>
<td>8.02±3.09</td>
<td>2.55</td>
<td>Very good</td>
</tr>
<tr>
<td>HSG</td>
<td>CBZ+PVPK29/32(5%)</td>
<td>25.1</td>
<td>29.4±1.1</td>
<td>1.17±0.04</td>
<td>14.6±3.16</td>
<td>2.24</td>
<td>Good</td>
</tr>
<tr>
<td>HSG</td>
<td>CBZ+ PVPK90(5%)</td>
<td>25.3</td>
<td>29.4±0.7</td>
<td>1.16±0.02</td>
<td>13.9±2.08</td>
<td>2.32</td>
<td>Good</td>
</tr>
<tr>
<td>HSG</td>
<td>CBZ+HPMCE5(5%)</td>
<td>25</td>
<td>29.5±1.2</td>
<td>1.18±0.04</td>
<td>15.2±3.45</td>
<td>2.42</td>
<td>Good</td>
</tr>
<tr>
<td>FBG</td>
<td>CBZ+PVPK29/32(5%)</td>
<td>25.2</td>
<td>27.4±0.9</td>
<td>1.08±0.03</td>
<td>8.02±3.09</td>
<td>1.98</td>
<td>Very good</td>
</tr>
<tr>
<td>FBG</td>
<td>CBZ+ PVPK90(5%)</td>
<td>25.4</td>
<td>28.3±0.9</td>
<td>1.11±0.03</td>
<td>10.2±2.93</td>
<td>1.87</td>
<td>Very good</td>
</tr>
<tr>
<td>FBG</td>
<td>CBZ+HPMCE5(5%)</td>
<td>25.3</td>
<td>27.9±0.9</td>
<td>1.10±0.03</td>
<td>9.31±2.97</td>
<td>2.1</td>
<td>Very good</td>
</tr>
<tr>
<td>HMG</td>
<td>CBZ+PVPK29/32(5%)</td>
<td>25.2</td>
<td>34.6±1.5</td>
<td>1.37±0.06</td>
<td>27.1±3.21</td>
<td>1.19</td>
<td>Poor</td>
</tr>
<tr>
<td>HMG</td>
<td>CBZ+ PVPK90(5%)</td>
<td>25.3</td>
<td>34.1±1.2</td>
<td>1.34±0.04</td>
<td>25.8±2.64</td>
<td>1.22</td>
<td>Poor</td>
</tr>
<tr>
<td>HMG</td>
<td>CBZ+HPMCE5(5%)</td>
<td>25.2</td>
<td>30.9±1.3</td>
<td>1.22±0.05</td>
<td>18.4±3.45</td>
<td>1.21</td>
<td>Poor</td>
</tr>
<tr>
<td>-</td>
<td>CBZ PURE</td>
<td>25.1</td>
<td>44.2±1.2</td>
<td>1.76±0.04</td>
<td>43.2±1.55</td>
<td>0.21</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

The flow properties of the granules have been represented in Table 2. The flowability can be described from the Carr index or Housner ratio. Their values are considered as per USP to interpret the flow of granules. Though particle shape, size, nature, inter-particular friction, and density affect flowability, density has played a significant role here. Plain CBZ possesses a very low density that adds fluffiness to CBZ and reduces flowability. Fluid bed granules and extrusion spheronized granules have shown excellent granules flow due to their dense.
and large size. In contrast, the poor flow was confirmed by LSG and HMG. Granules prepared by HSG have exhibited a good flow.

*Flow function study of granules*

![Flow function curve of granulation techniques](image)

**Figure 4.** Schematic representation of the flow function curve of granulation techniques
Brookfield's Powder flow tester (PFT) has also evaluated the flow behavior of powder or granules but with a different approach. In this apparatus, the test was conducted by applying a uniaxial unconfined failure test over a wide range of consolidation stresses. Figure 4 represents the flow behavior of the granules prepared by mentioned granulation methods. The flow function curve has been described in the diagram by the plot of unconfined failure strength versus the consolidation stress. The flow factor determines the flowability of granules. The flow factor (ff) is the ratio of principal consolidation stress ($\sigma_1$) and unconfined yield strength ($\sigma_2$).

Table 3 Flow function values and flow behavior

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Flow function (ffc) value</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$ff_c&lt;1$</td>
<td>Non-flowing</td>
</tr>
<tr>
<td>2</td>
<td>$1&lt;ff_c&lt;4$</td>
<td>Very cohesive</td>
</tr>
<tr>
<td>3</td>
<td>$2&lt;ff_c&lt;4$</td>
<td>Cohesive</td>
</tr>
<tr>
<td>4</td>
<td>$4&lt;ff_c&lt;10$</td>
<td>Easy flowing</td>
</tr>
<tr>
<td>5</td>
<td>$10&lt;ff_c$</td>
<td>Free-flowing</td>
</tr>
</tbody>
</table>

Table 3 indicates the relation between flow function values and the type of flow. The granules produced by ES and FBG were found in the free-flowing region. HSG and HMG methods were fitted into the easy-flowing region. LSG has confirmed a cohesive flow of granules. Previously from Figure 3, LSG and HSG have exhibited the highest friability. The higher friability effects on granule's flow due to the generation of fines. These fines act as an obstruction during flow. Similarly, PVP k 29/32 polymer also reported poor strength of granules due to weak binding capacity. Hence, further study was continued with only three methods: ES, FBG, HMG with PVP K90, and HPMC E5.

Nature of granule

SEM characterization
Granule’s morphology was analyzed by the SEM, as shown in Figure 5. It was found that fluid bed granules have confirmed the more uniform and spherical granules justifying better flow (refer to Figure 4.). The shear stresses during the extrusion process imparted a non-spherical shape to HMG granules resulting in a poor flow. The non-spherical, irregular shape of HMG granules can be observed in Figure 5. ES method has produced the relatively denser, cylindrical, and larger granules with improved granules flow.

**X-ray diffraction study**
Figure 6. X-ray diffractogram overlay of granulation techniques

XRD is the technique that analyzes the nature of the material. Figure 6. indicates the X-ray diffractogram of the granules. Usually, crystalline material exhibits a sharp hump in diffractogram during the analysis of the sample. HMG has successfully converted crystalline structures of granules into an amorphous form as no sharp hump was observed in the XRD diffractogram. Shear stress, friction between particles, and friction between screw and barrel of extruders were responsible for the rupture of crystals structure. ES and FBG have retained the crystalline nature of granules. The Diffractograms of the FBG and HMG are similar to the physical mixture (PM). It reveals that FBG and ES granules have retained their structure without any polymorphic conversion. Usually, CBZ undergoes spontaneous hydration with
water, but subsequent drying after granulation might have removed water molecules and stopped further conversion.

Additionally, Aeropal 300 pharma was added to the formulation to control the humidity effect. All obtained granules were packed in double-layered plastic bags then sealed into aluminum bags. All samples of aluminum bags were stored in HDPE bottles with silica to avoid moisture contamination.

3.2.3 Differential scanning colorimetry

![DSC overlays of granulation techniques](image)

**Figure 7.** DSC overlays of granulation techniques

DSC is the thermoanalytical method that determines the crystallinity of the sample. The crystallinity of the sample is evaluated by quantifying the heat of fusion during the melting of polymers. DSC generates a sharp endothermic peak during the melting of crystalline samples. In Figure 7, granules obtained from ES and FBG validate their crystalline nature justifying XRD results. The absence of a sharp endothermic peak was notified in the granules prepared from the HMG, which validates amorphous conversion.

*Powder flow tester characterization*

*Compressibility study of granules*
Consolidation is a densification process in which powder or granules are transferred into the material with minimum void or pores. Figure 8 shows no significant density changes in granules prepared by the ES, justifying their incompressible nature. Granules produced by FBG and HMG have shown a compressible nature. Rearrangement of the particles was significantly observed after applying consolidation stresses beyond 1kPa (from Figure 8), supporting the relatively more brittle nature of FBG and HMG granules. The outcome suggests ES granules can be packed in a plastic bag due to their robust nature, whereas care must be taken for granules obtained from FBG and HMG. Plastic containers are preferable for the packaging of such materials preventing wear and tear of granules.

**Effective angle of internal friction study**

![Effective angle of internal friction study](image)

Figure 9. Schematic representation effective frictional angle curve of granulation techniques
The internal angle of friction is the angle at which a sample can slip on its surfaces. In Figure 9., granules prepared by FBG have shown frictional angle in the range of 30-40° with fewer variations. In contrast, ES and FBG granules showed a comparatively higher effective angle of friction. The HMG process has been identified with significant variation in effective frictional angle due to the irregular shape of granules. On the other hand, the ES method has generated comparatively cylindrical granules that might have enhanced the effective angle of granules. Thus, the easier flow of the granules can be correlated with a reduction in frictional angle. Hence, FBG granules have exhibited free flow (Figure 4.) than ES and HMG granules.

Arching and rathole study of granule

![Graph showing arching and rathole parameter of granulation techniques](image)

**Figure 10.** Arching and rathole parameter of granulation techniques

Rathole and arching are the obstructions observed during flow from the vessels. The powder gets stuck above the outlet discharge in ratholing, leaving a stable internal structure in the core flow vessel. In the case of arching, the arch is formed above the outlet that stops the flow. As a result, arching is usually observed in mass flow vessels. Arching and rathole are the results of combined factors. The factors include inter particular friction, friction between particles and surfaces of the equipment, the mechanical interlocking of granules (granular shape), liquid bridging, cohesive forces developed, moisture, gravitational effect, fine concentration, temperature, etc. 19. From Figure 10., Granules produced by HMG followed by ES have shown higher arching dimensions and rathole diameters due to their non-spherical, irregular shapes.

In contrast, granules prepared from FBG have exhibited the lowest arching dimension and rathole diameter. In addition, the spherical nature of FBG granules might have reduced inter particular friction, friction between granules with the surface of hopper, and the prevention of...
mechanical interlocking of granules. Therefore, the FBG process has confirmed better bulk handling due to minimum rathole and arching requirements.

**Evaluation of tablet parameters**

**formulation of tablet**

Table 4. Formulation of granulation technique for tabletting

<table>
<thead>
<tr>
<th>Method</th>
<th>ES</th>
<th>FBG</th>
<th>HME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>CBZ</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>PVPK90</td>
<td>2.5</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>PEG 400</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>64.3</td>
<td>64.3</td>
<td>64.3</td>
</tr>
<tr>
<td>Water</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Aeropal 300</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4 represents the formulation of tablets prepared ES, FBG, and HMG granules. There were six types of tablets made with PVP K90 and HPMC E5 as binders. Aeropal 300 pharma was added as a moisture scavenger, and lactose was used as filler. Magnesium stearate was also added in formulation to decrease the hardness of the tablets.

**3.4.2 Weight, thickness, and hardness of tablets**

Table 5. Weight, friability, and hardness of tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight (avg)</th>
<th>% RSD</th>
<th>Friability (%)</th>
<th>% RSD</th>
<th>Hardness (N)</th>
<th>% RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.41</td>
<td>0.54</td>
<td>0.27</td>
<td>0.7</td>
<td>76</td>
<td>1.18</td>
</tr>
<tr>
<td>B</td>
<td>0.40</td>
<td>0.43</td>
<td>0.31</td>
<td>0.8</td>
<td>82</td>
<td>0.98</td>
</tr>
<tr>
<td>C</td>
<td>0.42</td>
<td>0.46</td>
<td>0.51</td>
<td>0.6</td>
<td>57</td>
<td>0.67</td>
</tr>
<tr>
<td>D</td>
<td>0.41</td>
<td>0.43</td>
<td>0.57</td>
<td>0.7</td>
<td>52</td>
<td>0.54</td>
</tr>
<tr>
<td>E</td>
<td>0.41</td>
<td>0.37</td>
<td>0.43</td>
<td>0.9</td>
<td>69</td>
<td>0.78</td>
</tr>
</tbody>
</table>
The evaluation was done by testing ten tablets for each parameter. Capping, lamination, or sticking was not observed from A to F (Table 5). But ES granules exhibited hardness during tableting due to their denser nature. In addition, PVP K90 and HPMC E5 binders helped to enhance the compactibility and tableting process.

Content uniformity, drug release, and stability study of tablets

Table 6. Content uniformity of tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mean tablet Assay (%)</th>
<th>% RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CBZ</td>
<td>98.49</td>
</tr>
<tr>
<td></td>
<td>PVPK90</td>
<td>98.60</td>
</tr>
<tr>
<td>B</td>
<td>CBZ</td>
<td>98.29</td>
</tr>
<tr>
<td></td>
<td>HPMC E5</td>
<td>98.41</td>
</tr>
<tr>
<td>C</td>
<td>CBZ</td>
<td>98.97</td>
</tr>
<tr>
<td></td>
<td>PVPK90</td>
<td>98.93</td>
</tr>
<tr>
<td>D</td>
<td>CBZ</td>
<td>98.89</td>
</tr>
<tr>
<td></td>
<td>HPMC E5</td>
<td>98.59</td>
</tr>
<tr>
<td>E</td>
<td>CBZ</td>
<td>98.35</td>
</tr>
<tr>
<td></td>
<td>PVPK90</td>
<td>98.11</td>
</tr>
<tr>
<td>F</td>
<td>CBZ</td>
<td>98.56</td>
</tr>
<tr>
<td></td>
<td>HPMC E5</td>
<td>98.70</td>
</tr>
</tbody>
</table>

**Figure 11.** The drug release profile of CBZ granules by ES, FBG, and HMG methods
Table 6. has confirmed content uniformity data within acceptable limits. More than 98% tablets assay was recorded by all formulation batches with the relative standard deviation below 0.89%. The drug release profile of CBZ granules (Figure 11) prepared by HMG, FBG, and ES reveals that the dissolution rate of CBZ granules was faster than CBZ tablets (Figure 12). Compression during tableting has reduced the dissolution rate. Compression increases hardness reduces porosity and surface area of the entity interacting with dissolution medium. From Figure 11, The complete release of pure CBZ was observed in 120 min. HMG has recorded a relatively fast release that confirms significant solid dispersion has been achieved. Dispersive, distributive mixing, and amorphous conversion are the major factors behind dissolution enhancement during the HMG process. FBG granules also exhibited better release. ES has reported a delay in the release due to the greater and denser particle size of ES granules. PVP K90 binder has shown a relatively faster release than HPMC E5 in all used techniques.

Table 7. Stability study of CBZ formulation.

<table>
<thead>
<tr>
<th>Code</th>
<th>0 days</th>
<th>30 days</th>
<th>60 days</th>
<th>90 days</th>
<th>180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dc(%)</td>
<td>Dr(%)</td>
<td>Dc(%)</td>
<td>Dr(%)</td>
<td>Dc(%)</td>
</tr>
<tr>
<td>A</td>
<td>98.66</td>
<td>98</td>
<td>97.39</td>
<td>97.14</td>
<td>97.1</td>
</tr>
<tr>
<td>B</td>
<td>98.24</td>
<td>96</td>
<td>95.65</td>
<td>93.79</td>
<td>95.12</td>
</tr>
<tr>
<td>C</td>
<td>98.94</td>
<td>95</td>
<td>97.84</td>
<td>93.12</td>
<td>96.13</td>
</tr>
</tbody>
</table>
In table 7, $D_C$ denotes drug content, and $D_R$ represents drug release from drug content. A slight reduction in the drug content and drug release with time was observed, but no significant changes were reported during the stability study.

**Conclusions**

Relatively denser and stronger granules were confirmed by ES, FBG, and HMG. ES followed by FBG has reported the free-flow of the granules. In contrast, the HMG has indicated a very cohesive flow of granules. The minimum rat hole and arching values of FBG and ES have disclosed their good bulk handling potential. The in-compressible nature of ES granules has added robustness for hassle-free packing and transport. HPMC E5 and PVP K90 binders have imparted more strength to granules than PVP K29/32. The HMG has successfully converted the amorphous structure from the crystalline form and achieved faster drug release within 80 minutes. Thus, the HMG and FBG proved to be the most suitable platform for improved drug release, flow properties, and compactibility of CBZ granules.

**Author contribution**

All authors contributed equally in the conceptualization, investigation, administration, and manuscript writing for this project.

**Conflict of interests**

The author claims that there is no conflict of interest.

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**References**


