Strength enhancement of talc pellets by incorporation of high percentage of hydroxypropyl methyl cellulose

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ABSTRACT

The present work is an attempt to improve the strength of spherically agglomerated talc pellets (TP) by incorporation of high percentage of HPMC. Wet Spherical Agglomeration (WSA) of talc was carried out implementing 3² factorial design, wherein, concentration of HPMC 50 cps (20, 25, 30% w/w) and PEG 6000 (2.5, 5, 7% w/w) were selected as independent variables. Studies have demonstrated that, all pellet batches (TP1-TP9) had acceptable shape and flow characteristics comparable to sugar spheres. However, with increase in amount of HPMC, crushing force and tensile strength of pellets was improved to 6.002 N and 1.634 ± 0.125 MPa respectively (batch TP4). This has been supported by value of regression coefficient for HPMC ($\beta_2=27.433$), however, PEG contributed to reduction in crushing force ($\beta_1=-4.6$). It was interesting to note that, at highest amount of HPMC and least amount of PEG (TP7), crushing force required was less, reflecting role of bridging liquid (DCM) in the strength building. Although satisfactory improvements in the CF and handling properties of pellets have been noted at optimum amount of HPMC, further investigations are needed pertaining to effect of type, amount of bridging liquid and shear imparted by stirrer on strength of pellets.

Keywords: high strength, talc pellets, wet spherical agglomeration.

INTRODUCTION

In addition to customary applications of talc (diluent, lubricant and glidant), literature has revealed numerous attempts pertaining to its granulation and/or agglomeration. Initially, agglomeration of talc was carried out by Ho and Hersey by the process of agglomerative phase of comminution.[1] Later, Lin and Peck attempted preparation of talc agglomerates using polyvinyl pyrrolidone as a binder, to improve tabletability, reduce fluffiness and use as a placebo beads.[2,3] Herein, fluidized bed dryer was used to obtain agglomerates. However, handling characteristics, especially strength of granules, was poor in both studies. To overcome these limitations and explore novel applications of talc, we developed wet spherical agglomeration (WSA) technique for preparation of spherical talc pellets.[4,5] In this process, incorporation of hydroxypropyl methyl cellulose (HPMC) and polyethylene glycol (PEG) was carried out to impart strength and sphericity to pellets. Indeed, it was a successful attempt to prepare talc pellets as a potential coating substrate or inert cores, in design of multiple unit particulate system.

Since, WSA of talc Per se is a complex process involving numerous formulation and process variables like type and concentration of polymers, proportion of talc, polymers, amount of bridging liquid/good solvent/non solvent, distributing agent, processing time, speed of stirring etc. Customary approach cannot elucidate effectively the effect of formulation and process variables on pellet quality attributes. In findings, it has been noted that, change in concentration of HPMC, PEG and dichloromethane (DCM, bridging liquid) affected the sphericity of pellets, tensile strength etc. At concentrations, 12.5% w/w of HPMC and 5% w/w of PEG, good quality spherical pellets were obtained.[6] But, strength of pellets was not at par with sugar pellets (SP). It was significantly less than sugar pellets. However, studies revealed that, HPMC is a main contributor for spheronisation, strength building and deformation of talc pellets prepared by WSA.
Hence, it was thought to increase the strength of pellets without compromising sphericity objective by incorporation of maximum amounts of HPMC to the agglomeration process, and PEG to facilitate the agglomeration process. Systematic study was undertaken to elucidate the effect of high concentration of HPMC (20-30% w/w) and PEG (2.5-7.5% w/w) on agglomeration process. A $3^2$ factorial design was implemented to optimize the talc agglomeration process and the prepared talc pellets (TP) were subject to micromeritics, compression, compactibility studies etc. An extended release (ER) talc pellet based multiparticulate dosage form of glipizide, oral anti diabetic agent (GPZ, BSC II, dose 2.5 to 20 mg, t½ 2-4 hours) was developed and its comparison was made with marketed formulation.

**MATERIALS AND METHODS**

**Materials**

Hydroxypropyl methyl cellulose 50 cps and Surelease were gifted by Colorcon Asia Pvt. Ltd, (Mumbai, Maharashtra, India). Talc (Indian Pharmacopoeia grade) was supplied by Get-Rid Pharmaceuticals, Pune, Maharashtra, India). Polyethylene glycol 6000 (BDH chemicals, Mumbai, India), Sugar pellets (Shubheccha homeoparmacy, Kolhapur, Maharashtra, India), dichloromethane (Merck Ltd, Mumbai, India) were purchased locally and rest chemicals were of analytical grade.

**Methods**

**Experimental design**

A $3^2$ full factorial design was implemented to optimize the WSA of talc. Percentage of HPMC (X1) and PEG (X2) in TP were studied as independent variables. Total nine batches of TP obtained (TP1-TP9) were subject to studies like micromeritic, mechanical, compressional properties etc. The effects of independent variables on response variables were studied using the polynomial equation,

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2$$

Eq. (10)

Where Y is the response/dependent variable, $\beta_0$ is the arithmetic mean response of the nine trials, and $\beta_1, \beta_2, \beta_{12}, \beta_{11}$ and $\beta_{22}$ are the regression coefficients for the corresponding variable $X_1, X_2, X_{12}, X_{11}$ and $X_{22}$, which represents the average result of changing one factor at a time from its low to high value. The interaction term ($X_1 X_2$) shows how the response changes when two or more factors are simultaneously changed. The polynomial terms ($X_1 X_1$ and $X_2 X_2$) are included to investigate nonlinearity.

Further, data were subject to generate 3-D response surface using Systat-12. The coded levels of independent variables (HPMC and PEG) and their translation in terms of percentages have been given in Table I.

<table>
<thead>
<tr>
<th>Batch code/Runs</th>
<th>Independent Variable along with levels and actual percentages</th>
<th>$X_1$ (%) w/w of HPMC</th>
<th>$X_2$ (%) w/w of PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1</td>
<td>-1(20)</td>
<td>-1(2.5)</td>
<td></td>
</tr>
<tr>
<td>TP2</td>
<td>-1(20)</td>
<td>0(5)</td>
<td></td>
</tr>
<tr>
<td>TP3</td>
<td>-1(20)</td>
<td>+1(7.5)</td>
<td></td>
</tr>
<tr>
<td>TP4</td>
<td>0(25)</td>
<td>-1(2.5)</td>
<td></td>
</tr>
<tr>
<td>TP5</td>
<td>0(25)</td>
<td>0(5)</td>
<td></td>
</tr>
<tr>
<td>TP6</td>
<td>0(25)</td>
<td>+1(7.5)</td>
<td></td>
</tr>
<tr>
<td>TP7</td>
<td>+1(30)</td>
<td>-1(2.5)</td>
<td></td>
</tr>
<tr>
<td>TP8</td>
<td>+1(30)</td>
<td>0(5)</td>
<td></td>
</tr>
<tr>
<td>TP9</td>
<td>+1(30)</td>
<td>+1(7.5)</td>
<td></td>
</tr>
</tbody>
</table>

*indicates -1= low level, 0= intermediate level and +1= high level

**Process Development Studies**

The WSA process, reported earlier, was adopted to prepare TP.[6] Briefly, homogenous powder mixture of talc (20 g), HPMC, tween 80 (1.5% w/w) was transferred to morishima vessel and slurred in DCM (40 ml) for 1 minute to get homogenous slurry. To slurry, entire aqueous solution of PEG (100ml) was poured and stirring continued using stirrer (with modified blades) at 1600 ± 50 rpm, in presence of walled baffles. The stirring was continued until pellets were obtained and supernatant was clear. At the completion of agglomeration process, contents were decanted; pellets were separated and washed with water, and subject to drying at 37 °C for 24 hours.
Evaluation of Pellets

Shape Analysis

The photomicrographs of randomly selected 10 TP from each batch were taken by optical microscope and subject to length (L), width (W), perimeter (P) and area (A) measurements. From the measured data, the shape parameters like aspect ratio (AR), circularity factors, roundness factor (RF) and shape factor (SF) were obtained using the formulae given below, [7]

\[
AR = \left(\frac{L}{W}\right)
\]

Eq. (1)

\[
\text{Circularity Factor} = \frac{\pi (\text{Major axis})^2}{4 \times \text{area}}
\]

Eq. (2)

\[
RF = \frac{(P)^2}{12.56 \times \text{area}}
\]

Eq. (3)

\[
SF = \frac{(P''^2)}{P'}
\]

Eq. (4)

Where, \( P'' = 2\pi \left(\frac{A}{\pi}\right)^{1/2} \)

Micromeritic Properties

Particle size distribution of each batch of TP was studied by mesh analysis (Ro-Tap sieve shaker, Labtronics, Haryana, India). The mean geometric diameter was obtained graphically.[8] The angle of repose was determined by fixed-funnel free-standing cone method.[9] Carr’s compressibility index (CCI) and Hausner’s ratio (HR) were determined using bulk density apparatus (Lab Hosp, Mumbai, Maharashtra, India).[10]

Kawakita Analysis

The flowability and packability of the TP was studied using the Kawakita plot. The plot of number of tapping (n) versus the degree of volume reduction (n/c) was plotted. And, the values of constants ‘a’ and ‘b’ were calculated by using the following equation.[11] The ‘a’ value indicates total reduction in volume of pellets bed and ‘b’ value is inversely proportional to yield strength of pellets.

\[
\left(\frac{n}{C}\right) = \left(\frac{n}{a}\right) + \left(\frac{1}{ab}\right)
\]

Eq. (5)

Where, ‘n’ is number of tapping;

‘C’ is degree of volume reduction and \( C = \left(\frac{V_a - V_\infty}{V_0}\right) \)

Where, \( V_0 \) is initial volume before tapping and \( V_\infty \) is volume after tapping.

Crushing force (CF) and friability determination

SP and TP must have adequate mechanical strength to withstand the loads during compression. The CF was measured by Jaroz and parot’s mercury load cell method, as reported earlier.[12] Randomly selected ten pellets from each batch were subject to determination of CF. For friability Studies, 10 g of TP from each batch were subjected separately to attrition in ball mill for 30 minutes at 25 rpm. The amount passing through sieve number 60 (ASTM) was treated as fines. The friability was expressed in terms of the percentage weight loss of fines during the process. As compared to pellets sugar spheres tends to laminate during compression which further limit on its use.

Pressure- Relative Density study

The Pressure- Relative Density studies were performed according to the method reported by Heckel.[13] Intact pellets (500 ± 5 mg), on compaction, after 24 hours of relaxation, were subject to weight, diameter, and thickness measurements. The data obtained were subject to Heckel equation,
\[
\ln \left( \frac{1}{1 - rd} \right) = KP + A
\]
Eq. (6)

Where ‘rd’ is the relative density (packing fraction) of pellets, P is applied pressure, ‘K’ is the slope and A is the intercept on Y-axis. Reciprocal of slope K, is mean yield pressure (MyP).

**Pressure- Tensile Strength Relationship**

The data used for Heckel plot studies were used for pressure tensile strength (σₜ) relationship. The hardness of the compacts was determined by Monsanto-type hardness tester and σₜ was calculated using following equation.[14]

\[
\sigma_t = \frac{2F}{\pi Dt}
\]
Eq. (7)

Where, ‘D’ is diameter, and ‘t’ is thickness of compacts; and ‘F’ is the force required to break the compacts.

**Leuenberger Analysis**

Compression susceptibility (γ) and compactibility (σₜmax) of pellets were assessed from Leuenberger analysis. The values of γ and σₜmax were obtained using the data for Pressure- relative density and tensile strength, using the equation given below.[15]

\[
\sigma_i = \sigma_{\text{max}} \left[ 1 - e^{(\gamma rd)} \right]
\]
Eq. (8)

Where, P is pressure and rd is the relative density.

**Elastic Recovery**

The elastic recovery of compacts was determined using the formula, [16]

\[
\% \text{ ER} = \left( \frac{t_{\text{max}} - t}{t} \right) \times 100
\]
Eq. (9)

Where, \( t_{\text{max}} \) is the thickness of the ejected tablet after 24 hours of relaxation and \( t \) is the thickness of the tablet immediately after ejection.

**Moisture Content**

The moisture content of TP4 was estimated using IR moisture balance (Rajdhani, Mumbai, India). 5 g of talc pellets were placed in heating pan and heated at a temperature of 105°C for 4 hours. The percent weight reduction due to moisture loss was directly displayed on the scale.

**Microbial Contamination**

A dispersion of TP4 prepared aseptically in water was inoculated in nutrient blood and McConkeys agar media and incubated at 37°C for 4 hours. These culture media plates were observed for the growth of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella* genus. Same dispersion was inoculated in sabourads media and incubated at 25°C for 48 hours for checking the growth of fungus.[17]

**Functionalisation of talc pellets**

**Layering of pellets**

The optimized batch TP4 was subject to drug layering by pan coating process. Glipizide (GPZ) is water insoluble drug but considering advantages of aqueous coating over organic coating, aqueous coating was selected as a method of choice. 50 g of uniform size pellets (16/20# mesh fraction with average size 1026.5 µm) were loaded into coating pan (Space Lab, Nasik, Maharashtra, India). Exactly weighed 1.66 g of finely micronized GPZ (10 mg/300 mg TP) was uniformly dispersed in aqueous dispersion of 3% w/v of PVP K-30 to make final volume 50 ml. Drug suspension was layered over it at a flow rate of 10 ml/hr using spray gun (Labultima, Mumbai) with nozzle tip diameter of 0.8 mm through a distance of 10 cm from pellet bed. Subsequently aqueous solution of HPMC 6 cps (2.5% w/v) was applied as a base coat up to a weight gain of 3% at 58 ± 2°C. Over the base coat functional coat of sustained release polymers was applied to achieve weight gain of 15% w/v. Thus the drug loaded pellet batch (LP4) was obtained.
**PXRD and DSC studies**

The powder X-ray diffraction patterns of Glipizide and LP4 were recorded separately (Philips X-ray diffractometer, PW-3710, Holland) and interpreted for any polymorphic or crystallinity change in the glipizide.

DSC-thermograms of glipizide and LP4 were obtained by using a DSC. (TA-60 instruments, Schimadzu). Calcium oxalate was used as standard to calibrate the DSC temperature and enthalpy scale. Samples were hermetically sealed in an aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60 mL/min. Heating was done from 10°C to 300°C at rate of 10°C/min.

**Scanning Electron Microscopy (SEM)**

For further details of shape and surface, photomicrographs were taken by scanning electron microscope (Jeol, JSM 6360, Japan) at an original magnification of X40, X60, X100, and X2000. Before taking the photographs the sample of bead was coated with gold in an argon atmosphere by an ion sputter coater (Jeol, JSM 1260, Japan) (Current: 20 mv and time: 120 seconds).

**Micromeritic Properties and Shape Analysis**

AR, CCI and HR studies were performed on LP4 using aforesaid described methods for TP4. Similarly, for shape analysis, photomicrographs of randomly selected 10 pellets were taken and analyzed.

**Drug Content**

Five gram pellets from LP4 were taken and powdered finely. The powder equivalent to 15 mg of GPZ was dissolved in 50 ml of methanol. The contents were filtered and 5 ml filtrate was further diluted to 50 ml using methanol. The absorbance of resulting solution was measured at 274 nm, using methanol as blank. The drug content was calculated taking 237 as the value of \( A \) (1%, 1 cm) at the maximum at 274 nm.

**In Vitro Drug Release Studies**

Exactly weighed 366 ± 0.5 mg of pellets from LP4, equivalent to 10 mg of GPZ were subjected to drug release studies (n=3) in USP type II dissolution test apparatus (TDT 08 L, Electrolab, Mumbai, India) in 900 mL of 0.1N HCl for first 2 hours followed by phosphate buffer (pH 6.8) for next 10 hours (37 ± 0.5°C and 75 rpm). 5 ml aliquots were withdrawn for analysis and replaced by equivalent amount of blank. The samples were analyzed at 274 nm by double beam UV visible spectrophotometer (Jasco V-530 UV). The data obtained were put in PCP Disso V 3.0 (Pune, India) software to type the drug release kinetics.

**RESULTS AND DISCUSSION**

**Process Development Studies**

For all batches of pellets (TP1-TP9) the processing time was found ranging from 39-64 min. and the percentage yield, was 88.73-99.71 w/w, both got decreased with increasing concentration of HPMC and PEG.\[18\] The trend has been supported by the values of regression coefficient \( \beta_1 \) and \( \beta_2 \) (Table II).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Regreation coefficient</th>
<th>( \beta_0 )</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
<th>( \beta_{11} )</th>
<th>( \beta_{22} )</th>
<th>( \beta_{12} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Percentage Yield</td>
<td>93.177</td>
<td>-1.064</td>
<td>-1.6</td>
<td>1.004</td>
<td>-0.136</td>
<td>-0.074</td>
</tr>
<tr>
<td>2.</td>
<td>Mean geometric diameter (MGD)</td>
<td>905.556</td>
<td>-45</td>
<td>15</td>
<td>1.667</td>
<td>1.667</td>
<td>-7.5</td>
</tr>
<tr>
<td>3.</td>
<td>Kawakita constant 'a'</td>
<td>0.149</td>
<td>0.013</td>
<td>-0.01</td>
<td>-0.016</td>
<td>-0.008</td>
<td>0.011</td>
</tr>
<tr>
<td>4.</td>
<td>Kawakita constant 'b'</td>
<td>0.132</td>
<td>0.001</td>
<td>-0.004</td>
<td>0.006</td>
<td>0.012</td>
<td>-0.012</td>
</tr>
<tr>
<td>5.</td>
<td>Crushing Force</td>
<td>606.044</td>
<td>-4.6</td>
<td>27.433</td>
<td>-46.26</td>
<td>-7.967</td>
<td>5.95</td>
</tr>
<tr>
<td>6.</td>
<td>% Weight Loss</td>
<td>0.164</td>
<td>0.072</td>
<td>-0.026</td>
<td>-0.014</td>
<td>-0.009</td>
<td>0.008</td>
</tr>
<tr>
<td>7.</td>
<td>Mean yield pressure (MyP)</td>
<td>1.58</td>
<td>0.061</td>
<td>0.09</td>
<td>0.02</td>
<td>-0.095</td>
<td>-0.174</td>
</tr>
<tr>
<td>8.</td>
<td>Tensile Strength</td>
<td>2.354</td>
<td>0.219</td>
<td>0.299</td>
<td>-0.286</td>
<td>-0.272</td>
<td>0.027</td>
</tr>
<tr>
<td>9.</td>
<td>Compactibility (( \sigma_{max} ))</td>
<td>2.19</td>
<td>0.189</td>
<td>0.265</td>
<td>-0.278</td>
<td>-0.253</td>
<td>-0.008</td>
</tr>
<tr>
<td>10.</td>
<td>Compression Susceptibility (( \gamma ))</td>
<td>0.965</td>
<td>0.082</td>
<td>0.037</td>
<td>-0.107</td>
<td>0.257</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Evaluation of Pellets**

**Shape Analysis**

For pellets, the values of AR, in the range of 1 to 1.2 are acceptable for sphericity (table III).\[19,20\] Especially for batch TP4 and TP7, the AR values are close to 1, underlining the role of low level of PEG in sphericity. Circularity factor, shape factor and RF gave further evidence of sphericity with values close to unity, equivalent to perfect...
sphere, for TP4. The comparison of TP4 with sugar pellets showed insignificant difference between the two with respect to AR, SF, Circularity factor and RF values at \( P < 0.05 \).

### Table III: Shape and sphericity parameters for talc pellets and sugar pellets*

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Aspect Ratio</th>
<th>Circularity Factor</th>
<th>Shape Factor</th>
<th>Roundness Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1</td>
<td>1.115 ± 0.052</td>
<td>1.035 ± 0.037</td>
<td>0.999 ± 0.000</td>
<td>1.000 ± 0.000</td>
</tr>
<tr>
<td>TP2</td>
<td>1.124 ± 0.128</td>
<td>1.084 ± 0.160</td>
<td>0.974 ± 0.067</td>
<td>1.069 ± 0.170</td>
</tr>
<tr>
<td>TP3</td>
<td>1.160 ± 0.126</td>
<td>1.114 ± 0.164</td>
<td>0.943 ± 0.064</td>
<td>1.137 ± 0.158</td>
</tr>
<tr>
<td>TP4</td>
<td>1.070 ± 0.029</td>
<td>1.010 ± 0.069</td>
<td>0.999 ± 0.000</td>
<td>1.000 ± 0.000</td>
</tr>
<tr>
<td>TP5</td>
<td>1.178 ± 0.064</td>
<td>0.939 ± 0.470</td>
<td>1.377 ± 0.998</td>
<td>0.947 ± 0.482</td>
</tr>
<tr>
<td>TP6</td>
<td>1.164 ± 0.107</td>
<td>1.218 ± 0.470</td>
<td>0.972 ± 0.047</td>
<td>1.064 ± 0.110</td>
</tr>
<tr>
<td>TP7</td>
<td>1.068 ± 0.282</td>
<td>1.218 ± 0.161</td>
<td>0.886 ± 0.021</td>
<td>1.274 ± 0.062</td>
</tr>
<tr>
<td>TP8</td>
<td>1.273 ± 0.198</td>
<td>1.438 ± 0.159</td>
<td>0.919 ± 0.063</td>
<td>1.197 ± 0.158</td>
</tr>
<tr>
<td>TP9</td>
<td>1.158 ± 0.049</td>
<td>1.280 ± 0.127</td>
<td>0.967 ± 0.04</td>
<td>1.077 ± 0.116</td>
</tr>
</tbody>
</table>

*indicates Average ± SD (n = 10).

### Figure I: SEM images of TP4 at magnifications of (A) 60X (B) 2000X.

**Micromeritic Properties**

The MGD of talc pellets was in the range of 850 - 970 µm, and was found to decrease with increase in PEG content and decrease in HPMC content (Table IV). The angle of repose \( (\theta) \) for all batches was found in the range of 25-30º, showing excellent flowability of pellets and it was found to increase with increase in PEG and HPMC content. CCI value was found to be 9.00 ± 0.70% and HR, below 1.25, showing excellent flowability of TP4. CCI was found maximum at highest levels of PEG. And, there was insignificant difference \( (P < 0.05) \) between batch TP4 and SP with respect to aforesaid parameters.

### Table IV: Data for Micromeritic and Mechanical Properties and of talc pellets*

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>MGD (µm)</th>
<th>AR (º)</th>
<th>CCI (%)</th>
<th>HR</th>
<th>Kawakita constants</th>
<th>% Weight Loss (Friability)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>‘a’</td>
<td>‘b’</td>
</tr>
<tr>
<td>TP1</td>
<td>940.33±</td>
<td>25.81±</td>
<td>11.66±</td>
<td>1.13±</td>
<td>0.12 ± 0.15 ±</td>
<td>5.13± 0.41 ±</td>
</tr>
<tr>
<td></td>
<td>3.51</td>
<td>0.22</td>
<td>1.17</td>
<td>0.02</td>
<td>0.00 ± 0.08 ±</td>
<td>0.00 ± 0.08 ±</td>
</tr>
<tr>
<td>TP2</td>
<td>950.66±</td>
<td>27.01±</td>
<td>10.00±</td>
<td>1.11±</td>
<td>0.11 ± 0.13 ±</td>
<td>5.44± 0.66 ±</td>
</tr>
<tr>
<td></td>
<td>5.17</td>
<td>0.33</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.02 ±</td>
<td>0.00 ± 0.02 ±</td>
</tr>
<tr>
<td>TP3</td>
<td>970.66±</td>
<td>28.16±</td>
<td>10.00±</td>
<td>1.11±</td>
<td>0.11 ± 0.15 ±</td>
<td>5.87± 0.83 ±</td>
</tr>
<tr>
<td></td>
<td>7.24</td>
<td>0.15</td>
<td>1.41</td>
<td>0.03</td>
<td>0.02 ± 0.05 ±</td>
<td>0.02 ± 0.05 ±</td>
</tr>
<tr>
<td>TP4</td>
<td>890.00±</td>
<td>26.39±</td>
<td>9.00±</td>
<td>1.09±</td>
<td>0.19 ± 0.13 ±</td>
<td>6.00± 0.51 ±</td>
</tr>
<tr>
<td></td>
<td>2.84</td>
<td>0.35</td>
<td>0.70</td>
<td>0.01</td>
<td>0.02 ± 0.06 ±</td>
<td>0.02 ± 0.06 ±</td>
</tr>
<tr>
<td>TP5</td>
<td>910.00±</td>
<td>27.43±</td>
<td>12.00±</td>
<td>1.13±</td>
<td>0.13 ± 0.13 ±</td>
<td>5.76± 0.71 ±</td>
</tr>
<tr>
<td></td>
<td>3.48</td>
<td>0.35</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.04 ±</td>
<td>0.00 ± 0.04 ±</td>
</tr>
<tr>
<td>TP6</td>
<td>920.00±</td>
<td>28.62±</td>
<td>12.00±</td>
<td>1.13±</td>
<td>0.10 ± 0.16 ±</td>
<td>5.90± 0.58 ±</td>
</tr>
<tr>
<td></td>
<td>5.11</td>
<td>0.60</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.04 ±</td>
<td>0.00 ± 0.04 ±</td>
</tr>
<tr>
<td>TP7</td>
<td>850.66±</td>
<td>27.68±</td>
<td>13.33±</td>
<td>1.15±</td>
<td>0.11 ± 0.17 ±</td>
<td>4.74± 0.45 ±</td>
</tr>
<tr>
<td></td>
<td>3.61</td>
<td>0.31</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01 ± 0.05 ±</td>
<td>0.01 ± 0.05 ±</td>
</tr>
<tr>
<td>TP8</td>
<td>860.33±</td>
<td>28.19±</td>
<td>12.00±</td>
<td>1.13±</td>
<td>0.16 ± 0.14±</td>
<td>5.72± 0.38 ±</td>
</tr>
<tr>
<td></td>
<td>4.15</td>
<td>0.10</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02 ± 0.05 ±</td>
<td>0.02 ± 0.05 ±</td>
</tr>
<tr>
<td>TP9</td>
<td>880.66±</td>
<td>29.21±</td>
<td>13.33±</td>
<td>1.13±</td>
<td>0.15 ± 0.13 ±</td>
<td>5.71± 0.44 ±</td>
</tr>
<tr>
<td></td>
<td>3.25</td>
<td>0.45</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 ± 0.06 ±</td>
<td>0.00 ± 0.06 ±</td>
</tr>
</tbody>
</table>

*indicates Average ± SD (n = 3).

**Kawakita Analysis**

The present study has demonstrated that, value of ‘a’ value is less than ‘b’ in all batches indicating, excellent flowability and densification (Table IV).
Crushing force (CF) and friability determination

Our previous study incorporating 12.5% w/w of HPMC, and using 5% w/w of PEG, have shown 4.91N CF giving rise to satisfactory pellets.[6] However, attempt to further enhance the CF has been successfully reflected in increase in CF, to 6.002 N, which is significantly high (P < 0.05). It was investigated that CF was increased, as anticipated, with increase in HPMC content, except for batch TP4, which showed highest CF even at intermediate level (25% w/w) of HPMC (Table IV). Because, at 30% w/w of HPMC levels, increase in CF was not noted. In TP4, highest CF might have been due to total entrapment of HPMC to TP and minimal loss of HPMC. And the amount of bridging liquid used might have been adequate/optimum for batch TP4, and would be inadequate for other batches, with 30% w/w of HPMC, wherein HPMC has to solvate in DCM, and thus, ensuring uniform distribution in the talc pellets. Figure II shows that CF of pellets was found maximum at low level of PEG, and was in agreement with earlier findings. The trend has been supported by values of regression coefficient for HPMC (β₂ = 27.433), and PEG (β₁ = -4.6). Although, there was significant difference between the values of CF for TP and SP (P > 0.05), satisfactory enhancement in CF has been noted. Means, in addition to HPMC, the role of bridging liquid is needed to be investigated in the strength building of pellets.

In friability study, the friability of SP was found to be nil because of its hard nature. Figure II shows that the friability of TP was increased with decrease in HPMC content and increase in PEG content, as anticipated.

Pressure-Relative Density Study

Mean yield pressure (MyP) in Heckel plot indicates the consolidation ability of pellets. HPMC was found responsible for increase in MyP value as seen in majority of batches. For all batches, MyP values were in the range of 1.2 to 1.9 tons which were higher than those reported earlier.[21] The MyP value was less in batch TP4, means had more consolidation ability.

Pressure- Tensile Strength Relationship

The present study has shown that, with increase in the amount of HPMC and PEG to talc pellets, TS has been increased, means, strength and extent of interparticulate bonding between solid particles has been enhanced. The contribution of HPMC and PEG both was almost equal (table II).

Table V: Data for compressibility and compactibility of talc pellets*

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Mean Yield Pressure (MyP) (Tons)</th>
<th>Tensile Strength (MPa) (σ₉₀₈₈)</th>
<th>Compactibility (γ)</th>
<th>Compression Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1</td>
<td>1.271 ± 0.170</td>
<td>1.381 ± 0.211</td>
<td>1.287</td>
<td>0.828</td>
</tr>
<tr>
<td>TP2</td>
<td>1.373 ± 0.341</td>
<td>1.755 ± 0.231</td>
<td>1.640</td>
<td>0.978</td>
</tr>
<tr>
<td>TP3</td>
<td>1.786 ± 0.364</td>
<td>1.858 ± 0.246</td>
<td>1.735</td>
<td>1.038</td>
</tr>
<tr>
<td>TP4</td>
<td>1.199 ± 0.078</td>
<td>1.634 ± 0.125</td>
<td>1.511</td>
<td>1.839</td>
</tr>
<tr>
<td>TP5</td>
<td>1.948 ± 0.198</td>
<td>2.481 ± 0.424</td>
<td>2.316</td>
<td>0.611</td>
</tr>
<tr>
<td>TP6</td>
<td>1.404 ± 0.095</td>
<td>2.392 ± 0.321</td>
<td>2.238</td>
<td>0.959</td>
</tr>
<tr>
<td>TP7</td>
<td>1.759 ± 0.075</td>
<td>1.742 ± 0.300</td>
<td>1.661</td>
<td>0.677</td>
</tr>
<tr>
<td>TP8</td>
<td>1.461 ± 0.065</td>
<td>2.241 ± 0.263</td>
<td>2.058</td>
<td>1.092</td>
</tr>
<tr>
<td>TP9</td>
<td>1.576 ± 0.134</td>
<td>2.323 ± 0.233</td>
<td>2.078</td>
<td>1.566</td>
</tr>
</tbody>
</table>

*indicates Average ± SD (n = 3).
Leuenberger Analysis
Findings suggest that, both the HPMC and PEG increased the compactibility of pellets. Table II shows that, compression susceptibility was maximum at highest content of HPMC and PEG.

Elastic Recovery
Large elastic recovery value indicates elastic deformation while small recovery value indicates plastic deformation. The recovery was in the range of 0.07 to 0.16% for all the batches and was insignificant.

Moisture Content
The moisture content of representative batch of talc pellets (TP4) after drying was found to be 0.214 ± 0.0114%.

Microbial Contamination
The microbial test performed on talc pellets did not show growth of harmful microorganism like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella* genus. The fungi growth also was not noted.

Functionalisation of Talc Pellets
**Layering of pellets**
In case of drug suspension layering more than 95% drug load was achieved (Table VI). Application of HPMC 6 cps, avoids direct contact of functional coat and active drug, and gives 3% weight gain. While, Surelease (aqueous dispersion of ethyl cellulose) as base coat demonstrated sustained release of glipizide at 15% weight gain.

**Table VI: Composition and Conditions of Coating Process (Pan Coating) for Talc pellets**

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Drug suspension layering (GPZ)</th>
<th>HPMC 6cps (2.5% w/v)</th>
<th>Surelease coat (15% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent weight gain</td>
<td>10 mg/300 mg beads</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Solvent composition</td>
<td>DW (50 mL) containing 3% w/v of PVP-K30</td>
<td>DW</td>
<td>DW</td>
</tr>
<tr>
<td>Coating pan speed</td>
<td>35 ± 2</td>
<td>40 ± 2</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>Inlet air temp. (°C)</td>
<td>60 ± 3</td>
<td>65 ± 3</td>
<td>65 ± 3</td>
</tr>
<tr>
<td>Product bed temp. (°C)</td>
<td>58 ± 2</td>
<td>63 ± 2</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>Flow rate (mL/hr)</td>
<td>12.5</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

*DW means distilled water

Figure III: (A) Overlain PXRD spectra of glipizide coated talc agglomerates (LP4), (B) Overlain DSC spectra of glipizide and coated talc agglomerates (LP4).
**PXRD and DSC studies**

PXRD showed that, the values of d spacing seen in pure drug GPZ have not been changed in LP4 (Figure IIIA). The reduction in number and intensity of peaks in case of LP4 was due to reduction in crystallinity of drug in suspension form, due to milling and dilution of drug. This concludes that, no any polymorphic change has taken place in GPZ during the coating process.

The DSC of GPZ has shown sharp endothermic peak corresponding to its melting point at 210.4 °C, and its energy has been reduced in LP4, may be due to dilution effect (Figure IIIB).

In addition to this, a small endothermic transition has been noted in LP4, at 60 °C due to T_g of the polymer system.

**Scanning Electron Microscopy (SEM)**

The SEM photographs revealed the finer surface characteristics of pellets demonstrating presence of small miniature pores on the surface of TP4 due to the channels formed during the diffusion and evaporation of DCM from the core to the pellet surface (Figure IB). While, of LP4 shows that uniform coat of polymer over the talc pellets resulting into a smooth surface, increased sphericity and disappearance of small pores observed on uncoated talc pellets (Figure IV).

![Figure IV: SEM images of LP4 at magnification of (A) 40X   (B) 100X.](image)

**Micromeritics and Shape Analysis**

The LP4 showed an angle of repose of (25.27° ± 0.84) which is less than for uncoated TP4. Similar observation has been made in case of Carr’s index (7.312 ± 0.278) and Hausner ratio (1.035±0.010). The sphericity parameters of coated pellets were AR: 1.094 ± 0.054, SF: 0.999, Circularity Factor: 1.073 ± 0.287 and RF: 1.000 ± 0.000. The pellets remained exactly spherical after the coating process (Figure IV A).

**Drug Content**

The drug content of LP4 was found to be 96.27 ± 2.34%. This was within the limit given by British Pharmacopoeia (90-110%) for GPZ formulation.[22]

**In Vitro Drug Release Studies**

From Figure V, it can be seen that LP4 and marketed sustained release formulation showed similar drug release profile. In first two hours of drug release study (0.1 N HCl), LP4 released about 19 ± 1.3% of drug while only 10 ± 0.76% of drug was released from marketed formulation. At the end of 12 hours, LP4 showed 94 ± 4% drug release while only 71 ± 8% of drug was released from marketed formulation. This increase in % drug release was because of more surface area of pellet exposed to dissolution medium. Both the formulations followed Higuchi-matrix release model throughout the entire study. It was revealed that drug release could be sustained from LP4 by increasing the thickness of functional coat of polymer. The similar findings have been noted for chlorpheniramine maleate loaded non-pareils at 12%, 17% and 21% coating levels.[23] Also the rapid release from hydrophilic core material (non-pareils) was noted, failing to sustain drug release showing importance of core material properties. As per USP, Sustain release tablets should release the stated amount of drug, after 1 hour: 0-15%; after 4 hours: 25-50%; after 9 hours: 50-75 % and 24 hours: NLT 85 %. Our formulation satisfies the condition (Figure V).
CONCLUSION

Significant improvements in strength of talc pellets (prepared by WSA), was successfully carried out by incorporation of higher % of HPMC. Factorial study demonstrated that, HPMC is not the sole contributor towards strength building, because, at highest amount of HPMC (30 % w/w), pellet strength reduction was noted, whereas, strength was maximum at 25 % w/w. Tensile strength improvements have been noted with increase in HPMC and PEG both. Since, amount of bridging liquid used was same in all batches of agglomeration, bridging liquid might have been inadequate, to solvate HPMC, thus lacking molecular networking of HPMC in pellets. Hence, further studies are needed to be undertaken to demonstrate the role of bridging liquid, along with HPMC, in strength building of pellets. Also the effect of shear imparted by stirrer on the consolidation of pellets and consequently strength needs to be investigated.

Acknowledgements

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REFERENCES


Figure V: Plot of cumulative % drug release of LP4 (blue) and Marketed formulation (pink) versus time.