Determination of Compressibility and In Vitro Release Properties of Acetaminophen Granules Coated with Eudragit E 30 D

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Acetaminophen is a drug which has a bitter taste and a short biological half life ($t_{1/2} = 2-3$ hours). There are two metabolites of acetaminophen in the body. The first form is the conjugation of glucuronic acid and the other is the hydroxylated form of the active metabolite. The second, hydroxylated metabolite is hepatotoxic in high concentrations (1,2). In order to avoid this effect, the rate of drug absorption must be slowed down.

In this study, we attempted to prepare acetaminophen granules by coating with a specific taste and odor masking acrylic polymer Eudragit E 30 D with the Fluidized bed process(3). Then, by direct compression method, tablets of these granules were prepared and consolidation and compressibility properties as well as in vitro release studies were investigated.

The acetaminophen particules were coated with fluidized bed (Glatt/Germany) using Eudragit E 30 D (Röhm Pharma GmbH/Germany). 250 g of acetaminophen were weighed. The concentration of the coating material was decided as 0.5 (C1), 3 (C2) and 5 (C3) % and dispersed in 50 ml distilled water. During the process, a nozzle having a diameter of 0.5 mm was used. The rate of the coating process was 5 ml/minute Eudragit E 30 D dispersion was sprayed 10 times/minute and the pressure of spraying air was 1.5 bar. After each spraying portion, in order to prevent agglomeration, the total amount was dried for 5 minutes at 70°C. After the coating process the whole mass was dried with hot air for 10 minutes. After the coating process of acetaminophen was completed the granules were formulated to prepare tablets.

The tablet formulation used is shown below:

\[
\begin{align*}
\text{Acetaminophen granules} & \quad 0.2 \text{ g} \quad 40 \% \\
\text{Avicel pH 101}^\text{®} \quad \text{(FMC Corp./USA)} & \quad 0.270 \text{ g} \quad 54 \% \\
\text{Precirol ATO 5}^\text{®} \quad \text{(Gattefosse/France)} & \quad 0.005 \text{ g} \quad 1 \% \\
\text{Ac-Di-Sol}^\text{®} \quad \text{(FMC Corp./USA)} & \quad 0.025 \text{ g} \quad 5 \%
\end{align*}
\]

The quantities indicated are calculated for 1 tablet. The mixing process was done in a cylindrical jar for 10 minutes in the turbula mixer.

Determination of consolidation properties of granules

The consolidation of 10 ml of each powder mixture was achieved in a 10 ml graduated cylinder with a funnel, so that percolation could be avoided. Then the weight of 10 ml was determined, the bulk density (BD) being calculated thereafter. The graduated cylinder was tapped with the help of the tapping instrument 5, 10, 20, 30, 40, 50, 75, 100, 200 and 300 times and the reduction in volume was measured. The natural logarithm of the tapping values ($N_t$), thus obtained was plotted against double (ln) the relative density change (A) (Equation 1)
and the parameters of the regression were determined with a computer programme (Basic 80) (Figure 1) (4).

\[
A = \frac{TD - BD}{TD} \quad \text{(Equation 1)}
\]

A: Relative density change  
TD: Tapped density  
BD: Bulk density

Information in the Kawakita equation:

\[
\frac{V_o - V_p}{V_o} = \frac{abP}{1 + bP} \quad \text{(Equation 3)}
\]

or,

\[
\frac{P}{C} = \frac{1}{ab} + \frac{1}{a} \cdot P \quad \text{(Equation 4)}
\]

C: Degree of volume reduction \((V_o - V_p / V_o = C)\)  
\(V_o\): Initial apparent volume of powder  
\(V_p\): Powder volume under applied pressure \((P)\)  
a, b: Constants, characteristic of the powder

In the Kawakita equation \((a)\) is a numeric parameter indicating the initial porosity of the compressed powder mass and \((b)\) is the compression coefficient.

**Determination of the compressibility of granules**

The compression properties of each mixed powder were investigated by using the HECKEL and KAWAKITA equations (5). For this purpose a 10 mm flat-faced punch and a hydraulic press were used. Equal volumes of granules \((1357.13 \text{ mm}^3)\) were pressed at \(767.0, 1150.5, 1534.0, 1917.5, 2301.0\) and \(3068.1 \text{ kgf/cm}^2\). When the desired pressure was reached, it was kept at this value for 20 seconds. The volume of the tablet; \(V_p\), formed at each pressure level was calculated. Results were calculated with a computer programme written using the Heckel and Kawakita equations (6).

**Heckel equation:**

\[
\ln = \frac{V_p}{V_p - V_w} = kP + \frac{V_o}{V_o - V_w} \quad \text{(Equation 2)}
\]

\(V_o\): Initial powder volume  
\(V_p\): The volume at each pressure value  
\(V_w\): The true volume of the solid (without pores)  
k: Constant. Heckel correlated the slope of the compaction curves, \(k\), with the yield strength of the material being compressed \((k = 1/\gamma)\)

**In vitro release rate studies**

In vitro release rate studies were employed to tablets using USP XXIV, (Method 2) paddle method \((37 \pm 0.5^\circ C, 50 \text{ rpm})\). pH 5.8 phosphate buffer solution was used as a dissolution medium and 4 ml's of aliquots were withdrawn at each interval and assayed at 241 nm with a Schimadzu UV – VIS 1201 spectrophotometer and dissolution profiles were determined (Figure 2) (7).

When consolidation and compressibility parameters of the formulations were evaluated, C3 gave the best results. In the Heckel equation, the largest \(r^2\) \((0.9285)\) and \(\gamma\) \((643.9 \text{ kgf/cm}^2)\) values belonged to this formulation (Tables 1, 2). Kawakita's \((a)\) value determined the greatest initial porosity in C3 formulation also.
When dissolution rate studies were evaluated, Figure 2 showed us that drug release rate slowed down with the increase in coating thickness (8). As a result, when acetaminophen particules were coated with different concentrations of Eudragit E 30 D, the consolidation and compressibility parameters were improved when compared to the drug itself. Also release rate of the drug was modified in all formulations when compared to the drug itself. Among the three formulations C3, which had Eudragit E 30 D at the highest ratio (5%), gave the best compressibility and release results.

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Table 1. The consolidation parameters.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.9027</td>
<td>257.2</td>
</tr>
<tr>
<td>C2</td>
<td>0.8548</td>
<td>370.7</td>
</tr>
<tr>
<td>C3</td>
<td>0.9285</td>
<td>643.9</td>
</tr>
</tbody>
</table>

Table 2. The compressibility parameters according to Heckel and Kawakita equations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>HECKEL</th>
<th>KAWAKITA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r^2 )</td>
<td>( P_y ) (kgf/cm²)</td>
</tr>
<tr>
<td>C1</td>
<td>0.9991</td>
<td>–0.9029</td>
</tr>
<tr>
<td>C2</td>
<td>0.9992</td>
<td>–0.9808</td>
</tr>
<tr>
<td>C3</td>
<td>0.9992</td>
<td>–0.9419</td>
</tr>
</tbody>
</table>

Figure 2. Dissolution profiles of tablets.
C* = Tablet without any coat

References