COMPARATIVE STUDY OF SUPERDISINTTEGRANTS USING ANTIEMETIC DRUG AS A MODEL

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Abstract:
In the present investigation comparison of three different superdisintegrants was carried out by formulating orally disintegrating tablets. Promethazine HCl was used as model drug which is an antiemetic drug. Sodium starch glycolate, croscarmellose and crospovidone were selected as superdisintegrants and each one was used in three different concentrations (2%, 3.5% and 5%). The drug-polymer compatibility was ruled out by FTIR studies. A total of nine formulations (PF1-PF9) were made by direct compression. All prepared formulations were evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time and in vitro drug release parameters. The results of the evaluation parameters for all the nine formulations of promethazine HCl were within the standard limits. The in vitro drug release for promethazine HCl tablets of all the formulations (PF1-PF9) was carried out using phosphate buffer pH 6.8 as dissolution medium. Among all the formulations the tablets formulated with crospovidone (PF7-PF9) have shown 91.43 - 98.43% (maximum) drug release at the end of 10 min than sodium starch glycolate and croscarmellose, hence from the present work, it concluded that among three superdisintegrants crospovidone is the ideal superdisintegrant for formulating oral disintegrating tablets for promethazine HCl.

Keywords: Superdisintegrants, promethazine HCl, sodium starch glycolate, croscarmellose, crospovidone

Introduction:
The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this problem, scientists have developed innovative drug delivery systems known as Orally Disintegrating Tablets (ODT). These are novel types of tablets that disintegrate/disperse/dissolve in saliva¹.

In order to formulate ODT we need special agents called as superdisintegrants. A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of some superdisintegrants are croscarmellose, crospovidone and sodium starch glycolate.

Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch glycolate, crospovidone and croscarmellose are some of the popular superdisintegrants. Superdisintegrants can act by 4 mechanisms namely swelling, wicking, repulsive force and deformation².

Ideal properties of superdisintegrants
Good Compressibility and Flow Properties
If the powders have 12-16% compressibility, they are said to have good flow powders. Crospovidones are significantly more compressible than other superdisintegrants.
Poor Solubility
The solubility of the major component in a tablet formulation can affect both the rate and the mechanism of tablet disintegration. Water soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally produce rapidly disintegrating tablets.

Poor Gel Formation Capacity
Gels can delay dissolution as the drug must first diffuse through the gel layer before being released into the body. Sodium starch glycolate is used as superdisintegrant in tablet formulation at a concentration of 4-6%.

Good Hydration Capacity
Drugs or other excipients, which are hydrophobic and could be adsorbed on disintegrant surfaces, adversely influence the extent of hydration and the effectiveness of these disintegrants. Addition of fast disintegrants of high hydration capacity is reported to minimize this problem, and therefore, enhance dissolution.

Complexation
Anionic disintegrants like croscarmellose sodium and sodium starch glycolate may complex with cationic drug actives and slow dissolution. Crospovidone a non-ionic polymer does not interact with cationic drug actives to retard drug release. The effects of superdisintegrants like croscarmellose sodium, sodium starch glycolate and polyplasdone XL on the dissolution behavior of several cationic drugs with varying water solubility reports that polyplasdone XL had a more rapid dissolution rate for the model cationic drugs, irrespective of their aqueous solubilities.

Materials and Methods
Promethazine HCl was obtained as gift sample from Mayer Healthcare Pharmaceuticals, Bangalore. Microcrystalline cellulose was obtained from SD fine chemicals. Sodium starch glycolate, croscarmellose and crospovidone were obtained from Shreeji chemicals, Mumbai. Talc, magnesium stearate was obtained from SD fine chemicals. Aspartame, raspberry flavor were obtained from SD fine chemicals.

Methods
In the present investigation direct compression method was employed for the formulation of orally disintegrating tablets of promethazine HCl with three different superdisintegrants in different concentrations (2%, 3.5% & 5%) for their comparative study. Promethazine HCl tablets are available in 25 mg and 50 mg doses in the market. Dose of 25 mg is selected for the present study. Microcrystalline cellulose was used as diluent, tcalc was used as glidant, magnesium stearate as lubricant, aspartame was used as sweetening agent and raspberry flavor was added to improve taste of tablets. The drug and the excipients were passed through #60-sieve. Weighed amount of drug and excipients except magnesium stearate were mixed in a mortar-pestle by geometric addition method for 20 min.

Evaluation of tablets
Thickness: The thickness of tablets was determined by using digital caliper (Coolant proof IP 65). The tablet is placed in between the two jaws of caliper scale and the reading was noted down. Three trials for each formulation were carried out.

Hardness: The tablet hardness, which is the force required to break a tablet was measured by using Pfizer hardness tester (S 14). Tablet is squeezed by two jaws. The first machines continually applied force with a spring and screw thread until the tablet started to break. When the tablet fractured, the hardness was read with a sliding scale. Three trials for each formulation were performed. The limit of hardness is 3-6 kg/cm².

Friability: Friability is the loss of weight of tablet in container/package due to removal of fine particles from
surface. This test is performed to ensure the ability of tablets to withstand shocks during processing, handling, transportation and shipment. The friability of tablets was determined using Roche friabulator (EF-2 USP). Ten tablets were initially weighed and transferred into the friabulator. The friabulator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The percentage friability of tablets was calculated using the following formula. The standard limit of friability is not more than 1%.

\[
\% \text{ Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100
\]

Weight variation: Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percentage deviation can be calculated using following formula.

\[
\% \text{ deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{Average weight}} \times 100
\]

Drug content: The drug content was estimated to know the percentage of drug present in the tablet. Twenty tablets were weighed and powdered. An amount of powder equivalent to 150 mg of promethazine HCl was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 249.60 nm using UV-Visible spectrophotometer (Shimadzu UV-1700).

In vitro drug release: In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (TDT 08L paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5 ºC at 50 rpm. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 5 ml were withdrawn at an interval of 2, 4, 6, 8 and 10 min. Samples were filtered through 10 µm filter. Same volume of the fresh dissolution medium was replaced every time. The collected samples were suitable diluted and analyzed at 249.60 nm by UV-Visible spectrophotometer (Shimadzu UV-1700) using dissolution medium as blank. The cumulative percentage drug release was calculated.

Results and Discussion:

The results of evaluation parameters for the nine formulations are shown in Table 2 & 3. The results of in vitro drug release of tablets for all the nine formulations are shown in Table 4, 5 and 6.

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (150 mg). The thickness of tablets from batch PF1-PF9 was found to be 2.50 - 2.86 mm and hardness was found to be 3.1 - 4.2 kg/cm². The friability of all the formulated tablets of promethazine HCl was found to be between 0.45 - 0.72 % and all the formulated tablets of promethazine HCl were shown the friability within the official limits. The weight variation for the tablets of all the (PF1-PF9) formulations was within the standard limits (±7.5%). All the formulated tablets (PF1-PF9) have shown in vitro dispersion time of less than 60 sec.
Among all the formulations, tablets prepared with crospovidone were shown less than 40 sec of dispersion time. The wetting time of all the formulations (PF1-PF9) are found to be within 39.30-68.33 sec which complies with the official limits. The drug content of all the nine formulations of promethazine HCl tablets was found to be within the range of 96.78-99.71% which was within the limits of IP specifications. The formulations PF1-PF3 were formulated with the help of sodium starch glycolate in concentration 2%, 3.5% and 5% respectively. The formulations PF4-PF6 were formulated with the help of croscarmellose in concentration 2%, 3.5% and 5% and the formulations PF7-PF9 were formulated with the help of crospovidone in concentrations 2%, 3.5% and 5% respectively. The formulations PF7-PF9 containing crospovidone shown 91.43-98.43% drug release which was the highest drug release compared to all the other formulations. The drug release profile for all the nine formulations are shown in Figure 1, 2 and 3.

Table 1: Formulation design of promethazine HCl orally disintegrating tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>Pf1</th>
<th>Pf2</th>
<th>Pf3</th>
<th>Pf4</th>
<th>Pf5</th>
<th>Pf6</th>
<th>Pf7</th>
<th>Pf8</th>
<th>Pf9</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSG</td>
<td>3</td>
<td>5.25</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Croscarmellose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>5.25</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Crospovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>5.25</td>
<td>7.5</td>
</tr>
<tr>
<td>Aspartame</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Raspberry flavour</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>Talc</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Magnesium stearate</td>
<td>3</td>
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<td>3</td>
<td>3</td>
<td>3</td>
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<td>3</td>
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<tr>
<td>MCC (q.s)</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
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</table>

Table 2: Results of thickness, hardness, friability and weight variation of promethazine HCl tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pf1</td>
<td>2.62±0.01</td>
<td>3.7±0.38</td>
<td>0.51</td>
<td>149.10±0.20</td>
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<tr>
<td>Pf2</td>
<td>2.63±0.07</td>
<td>3.4±0.33</td>
<td>0.48</td>
<td>151.09±0.33</td>
</tr>
<tr>
<td>Pf3</td>
<td>2.66±0.02</td>
<td>3.4±0.65</td>
<td>0.45</td>
<td>150.19±0.21</td>
</tr>
<tr>
<td>Pf4</td>
<td>2.63±0.05</td>
<td>4.2±0.25</td>
<td>0.72</td>
<td>150.33±1.76</td>
</tr>
<tr>
<td>Pf5</td>
<td>2.52±0.01</td>
<td>3.8±0.31</td>
<td>0.70</td>
<td>148.80±1.03</td>
</tr>
<tr>
<td>Pf6</td>
<td>2.53±0.05</td>
<td>3.8±0.72</td>
<td>0.67</td>
<td>150.33±2.12</td>
</tr>
<tr>
<td>Pf7</td>
<td>2.51±0.05</td>
<td>3.2±0.22</td>
<td>0.64</td>
<td>149.60±1.28</td>
</tr>
<tr>
<td>Pf8</td>
<td>2.50±0.05</td>
<td>3.1±0.30</td>
<td>0.60</td>
<td>150.43±1.71</td>
</tr>
<tr>
<td>Pf9</td>
<td>2.65±0.03</td>
<td>3.8±0.38</td>
<td>0.54</td>
<td>151.67±1.27</td>
</tr>
</tbody>
</table>

*Value expressed as mean ±SD, n=3
Keywords: Superdisintegrants, promethazine HCl, sodium starch glycolate, croscarmellose, crospovidone - D S Sandeep

Figure 1: In vitro drug release profile of promethazine HCl tablets formulated with sodium starch glycolate

Figure 2: In vitro drug release profile of promethazine HCl tablets formulated with croscarmellose

Figure 3: In vitro drug release profile of promethazine HCl tablets formulated with crospovidone

Conclusion:
A comparative study of three superdisintegrants (sodium starch glycolate, croscarmellose and crospovidone) was carried out using promethazine HCl as model drug by formulating nine batches (PF1-PF9) by direct compression method. The tablets were evaluated for parameters like thickness, hardness, friability, in vitro dispersion time, wetting time and percentage drug content. All the evaluation parameters of nine formulations were found to be within the IP limits. All the formulated tablets were examined for in vitro drug release studies. Among the three superdisintegrants, crospovidone showed maximum percentage drug release and hence it was found to be the ideal superdisintegrant for the formulation of promethazine HCl orally disintegrating tablets.

References: