Optimization of cross linked tragacanth and comparison of drug release rate profile with synthetic superdisintegrants on metoclopramide orodispersible tablets

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Abstract
Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. This fast dissolving tablet disintegrates instantaneously when placed on tongue and releases the drug dissolves or disperses in the saliva. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style. Present investigation is to optimize the cross linked tragacanth as natural superdisintegrants and comparison of drug release profile with SSG, Crospovidone by direct compression using metoclopramide hydrochloride. From the dissolution profiles, Optimized formulation found to be C3, 1:0.8 in ratio of Dry tragacanth powder and epichlorhydrin. Different drug formulations are prepared by direct compression. From the drug release profiles it is concluded that formulation with 4% of optimized CLT by direct compression have highest drug release of 95.39% at the end of 15mins when compare to other formulations and natural superdisintegrants have more efficiency than synthetic superdisintegrants.

Key-Words: Metoclopramide Hydrochloride, Cross Linked Trgacanth, SSG, Crospovidone

Introduction
Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Many conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration to obtained rapid and complete systemic drug absorption. Such immediate release products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Patients, particularly pediatric and geriatric patients, have difficulty in swallowing these solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.

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Material and Methods
Metoclopramide Hydrochloride was obtained as a gift sample from Wallace Pharmaceuticals Pvt. Ltd. Goa. Sodium starch glycolate was obtained from Micro labs, Bangalore; Crospovidone was obtained from Yarrow chemicals, Mumbai. All other chemicals used in the study were of analytical grade.

Methods
Optimization of cross linked tragacanth
A chemical method was used for the preparation of cross linked tragacanth. Dry tragacanth powder and epichlorhydrin in different ratios like 1:0.2, 1:0.5 and 1:0.8 were allowed to react at temperatures ranging from 37°C to 105°C. The reaction time was varied in between 45-100 min. The results also revealed that at 37°C, cross linking of tragacanth was not achieved at all the ratios tried in the present study. As the boiling point epichlorhydrin is 116°C, the cross linking reaction was carried out in the range of 60°C to 105°C. The temperature of cross linking reaction exhibited significant effect on the reaction rate. Based on the results of intrinsic properties, optimum conditions for cross linking of tragacanth were found to be
a) 1 : 0.8 ratio of tragacanth : epichlorhydrin,
b) Temperature of reaction as 105°C,
c) Time of reaction as 95 min.

\[
P-OH + Cl-CH_2-CH_2-Cl \rightarrow P-O-CH_2-CH_2-OP
\]

Where P-Polymer

Method of preparation of mixed blend of drug and excipients
All the materials were passed through sieve no. 60. Required quantity of each ingredient was taken for each specified formulation (Mentioned in the following table) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc).

Compression of tablets by using direct compression technique
Finally magnesium stearate and talc were added to the prepared blend. The mixed blend of drug and excipients was compressed into tablets weighing 200 mg using flat faced punches of 8 mm diameter in a rotary tablet press (Rimek mini press-1, Model RSB-4, Karnavati Engineering, Ahmedabad). A minimum of 50 tablets were prepared for each batch.

Evaluation of powder blend
Angle of repose
Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula.

\[
\theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

Bulk density
Apparent bulk density (ρ_b) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.

\[
\rho_b = \frac{M}{V_b}
\]

Tapped density
The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (ρ_t) was calculated using formula.

\[
\rho_t = \frac{M}{V_t}
\]

Compressibility index
The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) was calculated as follows.

\[
I = \frac{V_0 - V_1}{V_0} \times 100
\]

Where, V_0 is the bulk volume and V_1 is tapped volume.

Hausner’s ratio
Hausner’s ratio was an indirect index of ease of powder flow. It was calculated by the following method

\[
Hausner ratio = \frac{\rho_t}{\rho_d}
\]

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Evaluation of tablets
Characterization of Tablets for Physicochemical Parameters
The prepared Metoclopramide HCl Mouth Dissolving Tablets were evaluated for their physicochemical parameters like appearance, weight variation, hardness, friability, thickness and drug content.

Wetting Time and Water Absorption Ratio:
A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation.

\[
R = 100 \left(\frac{W_a - W_b}{W_b}\right)
\]

Where, Wb and Wa were the weights of the tablet before and after study.
In Vitro Dispersion Time:
In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson’s buffer pH 6.8. Three tablets from each formulation were randomly selected and in-vitro dispersion time was performed.

In-Vitro Disintegration Study
The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±1ºC as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±1ºC. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In-Vitro Dissolution Studies:
The In-vitro dissolution studies were carried out using USP apparatus type II (paddle) at 50 rpm. The dissolution medium used was pH 6.8 buffer (900 ml) maintained at 37 ± 0.5ºC. Aliquots of dissolution media were withdrawn at different intervals and content of Metoclopramide Hydrochloride was measured by determining absorbance at 273.20 nm.

Results and Discussion
Powder mixture of all the formulations were evaluated for various precompression parameters like bulk density, tapped density, Carr’s index and Hausner’s ratio using tap density apparatus. Bulk density was found in the range of 0.37-0.42 g/cm³ and tapped density between 0.45-0.48 g/cm³ as shown in the following table. Compressibility index was found to lie in the range of 8.31-17.50% with fair to good flow properties. Hausner’s ratio values are found in the range of 1.09-1.21. Flow properties of powder can be judged from the angle of repose. The angle of repose <30º indicates free flowing material and >40º with poor flow properties. The angle of repose were found in the range of 23.18º-28.32º as given in following table showing that the blend was free flowing and can be used for direct compression.

The formulated tablets are evaluated for the physiochemical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 2.4 to 3.5 Kg/cm² in all the formulations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 2.38 to 2.75 mm showing fairly uniform tabletting.

The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Orodispersible tablet. The values were found to be in the range of 18 to 39 sec. Wetting time was used as parameter to correlate with disintegration time. The cumulative drug release values after 15 minutes of dissolution were shown in the graphs. The graphical representation of the in-vitro disintegration time and wetting time, % cumulative drug release were shown in the figures.

Conclusion
From the dissolution profiles, Optimized formulation found to be C3, i.e. 1:0.8 in ratio of Dry tragacanth powder and epichlorhydrin. Different drug formulations are prepared by direct compression. From the drug release profiles it was concluded that formulation with 4% of optimized CLT by direct compression method have shows highest drug release of 95.39% at the end of 15mins when compare to other formulations and natural superdisintegrants after cross linked showed by have more efficiency than synthetic superdisintegrant.

Acknowledgement
The authors are thankful to Dr. Shivamurthy Muruga Sharanaru, President, S.J.M Vidya Peetha for providing all necessary facilities through the Principal, S.J.M college of Pharmacy, Chitradurga and also thankful to Wallace Pharmaceuticals pvt. Ltd. Goa for providing the gift sample of Metoclopramide.

References
5. Reeta R T.,“Unlimited scope for novel formulations as orally disintegrating systems:Present and future prospects”,

Table 1: Composition of Orodispersible Tablets of Metoclopramide Hydrochloride

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>OC₁</th>
<th>OC₂</th>
<th>OC₃</th>
<th>DS₄</th>
<th>DS₅</th>
<th>DC₆</th>
<th>DC₇</th>
<th>DCT₈</th>
<th>DCT₉</th>
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<tr>
<td>CLT</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>8</td>
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</tr>
<tr>
<td>SSG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>138</td>
<td>138</td>
<td>138</td>
<td>136</td>
<td>136</td>
<td>132</td>
<td>136</td>
<td>134</td>
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<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td></td>
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</tbody>
</table>

Each formulation contains 10mg of Metoclopramide, 40mg of MCC, 2mg of aspartame, 4mg of aerosil, 2mg of Mg.stearate.

Table 2: Data of preformulation studies

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose (θ)*</th>
<th>Bulk density (g/cm³)*</th>
<th>Tapped density (g/cm³)*</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC₁</td>
<td>25.82 ±0.249</td>
<td>0.3738±0.019</td>
<td>0.4531±0.017</td>
<td>17.50±1.72</td>
<td>1.2121±0.082</td>
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<tr>
<td>OC₂</td>
<td>27.16 ±0.315</td>
<td>0.4102±0.016</td>
<td>0.4593±0.024</td>
<td>9.62±1.81</td>
<td>1.1066±0.025</td>
</tr>
<tr>
<td>OC₃</td>
<td>26.64± 0.298</td>
<td>0.3827±0.034</td>
<td>0.4509±0.039</td>
<td>15.12±1.63</td>
<td>1.1782±0.038</td>
</tr>
<tr>
<td>DS₄</td>
<td>28.32± 0.341</td>
<td>0.4033±0.014</td>
<td>0.4763±0.017</td>
<td>15.32±1.67</td>
<td>1.1810±0.026</td>
</tr>
<tr>
<td>DS₅</td>
<td>27.46± 0.173</td>
<td>0.4152±0.045</td>
<td>0.4792±0.026</td>
<td>13.35±1.53</td>
<td>1.1541±0.023</td>
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<tr>
<td>DC₆</td>
<td>23.29± 0.198</td>
<td>0.4072±0.009</td>
<td>0.4837±0.032</td>
<td>15.81±1.72</td>
<td>1.1878±0.033</td>
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<tr>
<td>DC₇</td>
<td>25.45± 0.241</td>
<td>0.3947±0.049</td>
<td>0.4681±0.022</td>
<td>15.68±1.27</td>
<td>1.1859±0.062</td>
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<tr>
<td>DC₈</td>
<td>27.72± 0.372</td>
<td>0.4276±0.089</td>
<td>0.4664±0.037</td>
<td>8.31±1.37</td>
<td>1.0907±0.045</td>
</tr>
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Table 3: Results for the physical properties of tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (kg/cm²)</th>
<th>Uniformity of Thickness (mm)</th>
<th>Friability (%)</th>
<th>Uniformity of weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC₁</td>
<td>2.8 ±0.52</td>
<td>2.45 ±0.04</td>
<td>0.61</td>
<td>200.68 ±0.48</td>
</tr>
<tr>
<td>OC₂</td>
<td>2.4 ±0.5</td>
<td>2.38 ±0.05</td>
<td>0.64</td>
<td>200.26 ±0.45</td>
</tr>
<tr>
<td>OC₃</td>
<td>2.5 ±0.52</td>
<td>2.72 ±0.05</td>
<td>0.57</td>
<td>201.09 ±0.45</td>
</tr>
<tr>
<td>DS₄</td>
<td>3.2 ±0.46</td>
<td>2.47 ±0.03</td>
<td>0.52</td>
<td>200.94 ±0.36</td>
</tr>
<tr>
<td>DS₅</td>
<td>3.0 ±0.48</td>
<td>2.53 ±0.04</td>
<td>0.56</td>
<td>200.64 ±0.42</td>
</tr>
<tr>
<td>DC₆</td>
<td>3.5 ±0.54</td>
<td>2.48 ±0.06</td>
<td>0.52</td>
<td>202.13 ±0.44</td>
</tr>
<tr>
<td>DC₇</td>
<td>3.0 ±0.45</td>
<td>2.55 ±0.05</td>
<td>0.62</td>
<td>201.29 ±0.48</td>
</tr>
<tr>
<td>DC₈</td>
<td>2.7 ±0.55</td>
<td>2.42 ±0.03</td>
<td>0.54</td>
<td>200.58 ±0.42</td>
</tr>
<tr>
<td>DC₉</td>
<td>2.5 ±0.55</td>
<td>2.75 ±0.05</td>
<td>0.58</td>
<td>201.02 ±0.45</td>
</tr>
</tbody>
</table>

mean ± S.D., n=3 (all the values are the average of three determinations)
### Table 4: Results for the evaluation of tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug content (%)</th>
<th>Wetting time (sec)</th>
<th>In-vitro disintegration time (sec)</th>
<th>% cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC₁</td>
<td>99.02 ± 0.4</td>
<td>51</td>
<td>31</td>
<td>86.78 ± 0.7</td>
</tr>
<tr>
<td>OC₂</td>
<td>99.36 ± 0.2</td>
<td>44</td>
<td>27</td>
<td>88.04 ± 0.2</td>
</tr>
<tr>
<td>OC₃</td>
<td>99.82 ± 0.4</td>
<td>40</td>
<td>24</td>
<td>91.13 ± 1.2</td>
</tr>
<tr>
<td>DS₁</td>
<td>97.64 ± 0.3</td>
<td>56</td>
<td>39</td>
<td>77.65 ± 0.5</td>
</tr>
<tr>
<td>DS₂</td>
<td>98.91 ± 0.2</td>
<td>50</td>
<td>30</td>
<td>80.09 ± 0.8</td>
</tr>
<tr>
<td>DC₃</td>
<td>98.86 ± 0.4</td>
<td>52</td>
<td>34</td>
<td>82.47 ± 0.6</td>
</tr>
<tr>
<td>DC₄</td>
<td>99.18 ± 0.4</td>
<td>46</td>
<td>27</td>
<td>87.21 ± 1.2</td>
</tr>
<tr>
<td>DCT₃</td>
<td>99.69 ± 0.4</td>
<td>35</td>
<td>22</td>
<td>93.68 ± 0.4</td>
</tr>
<tr>
<td>DCT₄</td>
<td>98.91 ± 0.2</td>
<td>26</td>
<td>18</td>
<td>98.24 ± 1.4</td>
</tr>
</tbody>
</table>

**Fig. 1:** Graphical representation of *in-vitro* disintegration time and wetting time
Fig. 2: cumulative % drug release for the batches OC1-OC3

Fig. 3: cumulative % drug release for the formulations