Development of natural gum based fast disintegrating tablets of glipizide

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Dysphagia and risk of choking are leading causes of patient non-compliance in the self-administration of conventional tablets. To overcome these limitations of conventional tablets fast-disintegrating tablets were developed, using natural gums. Natural gums were evaluated for bulk swelling capacity. Powder mix containing natural gums and glipizide was evaluated for water sorption, swelling index and capillary action. For faster onset and immediate hypoglycemic action, the fast disintegrating tablets were prepared with various types of natural gums using the direct compression technique. Formulations containing guar gum disintegrated within a minute and fulfilled the official requirements for dispersible tablets. As the amount of guar gum increased, the friability increased and hardness decreased, resulting in a shorter wetting and disintegration time. Gum acacia and gum tragacanth did the opposite. The glipizide-loaded fast disintegrating tablet prepared with 18 mg of guar gum gave a friability of 0.46 ± 0.02%, content uniformity of 99.34 ± 0.82%, drug content of 99.15 ± 1.16%, wetting time of 39.0 ± 1.04 sec, hardness of 5.70 ± 1.41 Kg and disintegration time less than 30 sec, suggesting that it was a practical product with a good tablet property. In conclusion, natural gum based patient-friendly fast disintegrating tablets of glipizide can be successfully formulated.

Key words: Direct compression, fast disintegrating tablet, guar gum, natural gum

INTRODUCTION

Physiological and neurological conditions, such as dysphagia, risk of choking, and hand tremors are leading causes of patient non-compliance in the self-administration of conventional solid oral dosage forms. Solid dosage forms also present significant administration challenges in other patient groups such as children, mentally challenged and uncooperative patients and patients in reducing fluid diets. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients traveling without water, limit utility of orally administered conventional tablets. To overcome the above limitations of conventional solid dosage forms and treatment compliance fast-disintegrating tablets were developed, using jelly, water absorbing, and swelling-gelated materials or water-soluble polymers. Fast disintegrating tablets are a novel oral dosage form that quickly disintegrates in saliva without the need for water and can produce a rapid onset of action with best patient compliance. Interfacial solid/liquid interactions play a crucial role in the wetting, spreading and adhesion processes. Thus, the key properties of fast disintegration lie in the powder characteristic of tablet blend. Therefore, nature of powder or tablet blend drastically affects the disintegration time of fast disintegrating tablets. Fast disintegration of tablets in the mouth renders possibly a certain degree of absorption throughout the sublingual or the buccal mucosa. Moreover, drug candidates that undergo pre-gastric absorption when formulated as fast disintegrating tablets may show increased oral bioavailability. Fast disintegrating tablets are prepared by various techniques such as lyophilization, molding, and direct compression. Fast disintegrating tablets, prepared using the lyophilization technique, were disintegrated within about 30 seconds but offered a low physical resistance and high friability. Furthermore, the

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Glipizide, a sulfonylurea antidiabetic drug, is given orally in the treatment of type 2 diabetes mellitus and has duration of action of up to 24 hrs. The usual initial dose is 2.5 to 5 mg daily given as a single dose about 30 minutes before breakfast. Glipizide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring one to three hours after a single dose. It is extensively bound to plasma proteins and has a half-life of about two to four hours. It is metabolized mainly in the liver and excreted chiefly in the urine, largely as inactive metabolites. In the modern era natural materials are widely used in the pharmaceutical industries as disintegrants (e.g.,-Agar), hydrogels (e.g.,-guar gum), matrix formers (e.g.,-xanthan gum), binders (e.g.,-gum acacia), thickeners, water retention agents, emulsion stabilizers, suspending agents (gum acacia, gum tragacanth) and film formers.

In the present study, natural gum based patient-friendly dosage form was developed as a fast disintegrating tablet containing glipizide. Gums are pathological products, readily dissolve in water. Hence, gum acacia, gum tragacanth and guar gum were selected for the development of fast disintegrating tablets. The issue considered in the development of glipizide-loaded fast disintegrating tablet was to improve patient compliance by a tablet formulation that was easily administered by elderly, children, mentally challenged and uncooperative patients.

MATERIALS AND METHODS

Materials
Glipizide was obtained as a gift sample from Supra Chemical Pvt. Ltd. (Mumbai, India). Gum acacia, gum tragacanth, guar gum and microcrystalline cellulose were purchased from Merk Specialty Private Limited (Mumbai, India). Magnesium stearate and talc were purchased from Loba Chemie Private Limited (Mumbai, India).

Analytical method
Accurately weighed glipizide (100 mg) was placed in 100 ml volumetric flask and dissolved in the phosphate buffer (pH 7.4). 5 ml of this solution was taken in a 100 ml volumetric flask. For generating a calibration curve, 5 to 50 μg/ml of primary standard was prepared and the calibration curve was obtained by measuring their absorbance at predetermined UV-1800 spectrophotometer (Shimadzu, Japan) at 275 nm. Glipizide concentration was calculated using the linear regression equation of the calibration curve (Absorbance = 0.0234 × concentration + 0.0031, r² = 0.9993).

Powder evaluations

Bulk swelling capacity
A modification of the method described by Bowen and Vadino was used. Bulk swelling capacity studies were carried out on gum acacia, gum tragacanth and guar gum, separately. Each of powdered gum (2.0 g) was carefully poured into a 25 ml volumetric cylinder, and the bulk volume was measured (V1). 10 ml of distilled water was added. The suspension was well shaken for 5 min and volume is made up to 25 ml with distilled water. The samples were allowed to stand for 24 hrs, and the sedimentation volume was read off (V2). Three parallel measurements were carried out. The process was repeated with simulated gastric fluid and salivary fluid also. The bulk swelling capacity was calculated by the formula:

Swelling capacity = V2/V1  (1)

Water sorption time and swelling index
The drug excipient blend (50-100 mg) was filled into micropipette tips (transparent, 2 ml, Aldrich) for estimating water sorption time and swelling index. The tip outlet was first blocked with a tiny swab of nylon fiber to avoid any leakage of the powder during the experiment. After placing the solid sample into the tip, it was tapped 10 times by dropping on a hard surface from 10 cm height to obtain possibly the same packing of the bed. The plastic tip was weighed (Wa) then dipped into a 2-3 mm layer of distilled water. The time taken by the liquid to reach to the top of the powder bed was estimated at water sorption time. When the bed became wet with liquid, the tip was again weighed (Wb) to find the amount of the liquid taken in by the powder. The swelling index was estimated as:

SI=100 × (Wb-Wa)/Wa  (2)

Capillary action
Guar gum, gum acacia and gum tragacanth were blended with glipizide so that each contain 1.0, 3.0, 5.0, 7.0, 9.0, 12 and 15% w/w concentrations in glipizide. The powders were mixed geometrically. Powder blend was, respectively, filled in Perspex capillary tubes (diameter, 0.304 cm each). Each tube was tapped 20 times on tile in order to obtain a constant height of 7 cm of powder column. Bottom ends were plugged with an absorbent paper and stood-dipped in water by means of supports. Water uptake by column in the tube was observed and measured up to 30 minutes after the start of experiment.

Preparation of fast dissolving tablets
The raw materials were passed through a no. 100 screens before mixing and mixed using a glass mortar and pestle. The powder blends were lubricated with 1% wt/wt talc and 1% wt/wt magnesium stearate. The powder blends ready for
compression were transformed into tablets using a tablet punching machine (Cadmach, India) at a compression force of four tons.

Evaluation of tablets
Content uniformity test
For content uniformity test, representative samples of 10 tablets were randomly selected, and assayed individually by UV-1800 spectrophotometer (Shimadzu, Japan) at 275 nm. The required specification for this test is that uniformity of the dosage units should be within a range of 85-115% with a relative standard deviation of less than or equal to 6%.\(^\text{[29]}\)

Drug content analysis
A randomly selected tablet was crushed in a glass mortar and pestle, and the powdered tablet was suspended in 100 ml of phosphate buffer (pH 7.4) with stirring on a magnetic stirrer. After 24 hrs, the solution was filtered and the filtrate was analyzed by UV-1800 spectrophotometer (Shimadzu, Japan) at 275 nm. The drug entrapment efficiency\(^\text{[30]}\) was calculated using the formula:

\[
\text{Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100
\]

Hardness and friability
Monsanto hardness tester (Cadmach, Ahmedabad, India) was used to perform hardness test. For hardness test, six tablets were randomly selected from each batch. The friability test was performed using a Roche friabilator (Campbell Electronics, Mumbai, India). Randomly selected Samples of 20 tablets from each batch were tested at a time. After 100 turns, the tablet samples were evaluated by weighing.\(^\text{[29]}\)

Disintegration time
In vitro disintegration test for was determined using a modified disintegration test apparatus with distilled water as the disintegrating medium.\(^\text{[31]}\) A more suitable apparatus was developed because many reports\(^\text{[32-35]}\) indicated the unsuitability of the conventional disintegration test apparatus for rapidly disintegrating tablet. Briefly, the apparatus consisted of a glass beaker of 1000 ml capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 ml of disintegrating medium, the basket had only 6 ml of it. A magnetic bead was placed at the bottom of the beaker, set at 25 rpm, maintained at 37 ± 2°C.

Wetting time
Wetting time study of the tablet was carried out using the method reported\(^\text{[36]}\) with slight modification.\(^\text{[36]}\) A piece of tissue paper folded twice was kept in a culture dish (internal diameter 9 cm) containing 10 ml of distilled 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.

RESULTS AND DISCUSSION
Powder evaluation
Figure 1 showed bulk swelling study of guar gum, gum acacia and gum tragacanth. Bulk swelling study was performed in three different media, such as distilled water, simulated gastric fluid and salivary fluid. In all the media, guar gum showed better swelling capacity as compared to gum acacia and gum tragacanth. It was also found that all the three gums showed better swelling in distilled water than in simulated gastric fluid and salivary fluid. Water sorption time indicates the time required by the powder excipient blend to transport water inside the powder bed. Swelling study is a measure of the swelling capacity of the powder. Higher the swelling index, lower could be the disintegration time. Figures 2 and 3 showed the effect of guar gum, gum acacia and gum tragacanth on water sorption time and swelling index. Guar gum exhibited maximum swelling index and minimum water sorption time as compared to gum acacia and gum tragacanth. This suggested mucilaginous or gel-forming nature of gum acacia and gum tragacanth. Swelling substances\(^\text{[37]}\) that tend to be mucilaginous or gel-forming in water are not able to act as disintegrating agent. Such materials develop a viscous coat around the tablet, which hinder further movement of water into the tablet matrix. All the gums showed the minimum water sorption time as well as swelling index in simulated gastric fluid.

Figure 4a-c, showed capillary water uptake by glipizide-gum powder mix. In the column containing gum acacia and gum tragacanth, an initial rapid liquid uptake was observed, which then slowed down and finally stopped. Very less liquid uptake was due to the gel-forming nature of gum acacia and tragacanth. At low concentration of gum acacia (1 and 3%) and gum tragacanth (1, 3 and 5%) liquid uptake increased with time.

In the column containing 12 and 15% w/w of guar gum, gelling occurs upon the initial contact of powder mix and water, hence, further liquid uptake was prevented. In the column containing 9% w/w of guar gum, an initial rapid liquid uptake was observed, which then slowed down and finally stopped. In the column containing 5 and 7% w/w of guar gum, an initial rapid liquid uptake was observed, which then slowed down. In case of column containing 1 and 3% guar gum, liquid uptake was good [Figure 4a]. Guar gum normally forms gel during swelling, but its initial swelling could elicit disintegration action in the tablet before further liquid uptake results in more extensive swelling and gelling. In the column containing higher amount of guar gum, the uptake of liquid in these columns is found to be entirely dependent on the non-gelling (glipizide) component while gelling component (gum) swelled rapidly to form a coherent gel through which
liquid uptake occurred either very slowly or not at all. Best concentration of guar gum as a disintegrant was observed at 9% w/w, whereas the height of capillary uptake was maximum at 1 and 3% concentration, when swelling of gum was not enough to exert pressure so that the tablet could disintegrate. At a critical concentration (9% w/w) for disintegration time, particle of polymer occupy the minimum distance apart in tablet matrix, which permits rapid liquid penetration and does not allow the formation of the continuous gel network, as in case of higher concentration, which may hinder fluid diffusion.

**Evaluation of tablets**

The compositions of all the formulations were shown in Table 1. Formulations, F1 to F3 were prepared using gum acacia, F4 to F6 using gum tragacanth and F7 to F9 using guar gum in the concentration of 3, 6 and 9% of the total weight of the tablet. Table 2 summarizes the results for disintegration, wetting time, friability (%), hardness, content uniformity and drug content analysis of different formulations.

Hardness of the tablet increased with increase in concentration of gum acacia and gum tragacanth because of their binding effects on tablets. However, when guar gum was incorporated as disintegrant, hardness decreased with increase in concentration of guar gum. It was found that, tablet produced with guar gum were less hard than those produced with gum acacia and gum tragacanth. Tablets containing guar gum exhibited higher percentage friability as compared to the tablets containing gum acacia and gum tragacanth. The percentage friability of the tablet decreased with increase in concentration of gum acacia and gum tragacanth. This is because of the binding nature of gum acacia and gum tragacanth. Increase in concentration of guar gum showed increased percentage friability. In all the formulations, irrespective of the concentration of disintegrant used, friability index remained well within 1% w/w, an upper level of acceptability for pharmaceutical products.

Disintegration time and wetting time decreased with increasing concentration of guar gum but this was not true
in the case of tablets produced with gum acacia and gum tragacanth. It was found that tablets produced with guar gum took less time to disintegrate than those produced with gum acacia and gum tragacanth. Disintegration time data of the tablets produced with guar gum are comparable with tablets made with gum acacia and gum tragacanth, thereby indicating that guar gum could be used as a disintegrant. The studies revealed that the guar gum is likely to initiate disintegration action by swelling. It is possible that upon an initial contact between guar gum and water, particles swell thereby generating enough pressure to initiate the disintegration well before the gel is formed. List and Muazzam\textsuperscript{[38]} showed that a very slight increase in the volume of particles of disintegrant, which cannot be perceived by a visible increase in diameter of grains, could display sufficient force to activate disintegration.

Drug content was found to be uniform among different formulations and ranged from 99.07 ± 1.03 to 99.84 ± 0.67%. For the content uniformity test, the required specification is that uniformity of the dosage units should be within a range of 85-115% with a relative standard deviation of less than or equal to 6%. The average percentage deviation of all the prepared tablets was found to be within the above limit, and hence all formulations passed the content uniformity test as per the official requirements.

The most important parameter that needs to be optimized in the development of oral dispersible tablets is the disintegration time of tablets. Formulations containing gum acacia and gum tragacanth disintegrated in more than three minutes and not fulfilled the criteria for dispersible tablets whereas formulations containing guar gum disintegrated within a minute and fulfilled the official requirements (<3 min) for dispersible tablets. Among all batches of guar gum based formulations, batch F9 was selected as an optimized batch and explored further because of its lowest disintegration time, permissible percentage friability and acceptable hardness.

**Effect of guar gum concentration on disintegration time**

Figure 5 showed the effect of concentration of guar gum on disintegration time. The disintegration time was decreased as the concentration of guar gum increased from 1 to 12%. Shortest disintegration time was found in the formulation containing 12% guar gum. Increased disintegration time was found in the formulation containing 15% guar gum compared to the formulation containing 12% guar gum.

**Effect of compression force on disintegration time**

Figure 6 showed the effect of compression force on disintegration time. The disintegration time was increased with increasing the compression force. The disintegration time was more affected by compression force at low and high guar gum concentration. At intermediate guar gum concentration, compression force has little effect on disintegration time. The increase in compression force is responsible for reduced liquid penetration into the tablet structure and hence the increase tablet strength. This increase in tablet strength hampered liquid penetration and access to disintegrant particle and the development of an effective disintegrating force inside the tablets.

**Effect of amount and type of lubricant on disintegration time**

Figure 7 showed the Effect of amount and type of lubricant on disintegration time. It is known that magnesium stearate is hydrophobic while talc has hydrophobic and hydrophilic

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**Table 1: Formulation composition**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tbody>
<tr>
<td>Glipizide</td>
<td>mg</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>Gum acacia</td>
<td>mg</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gum tragacanth</td>
<td>mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guar gum</td>
<td>mg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Talc</td>
<td>mg</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>mg</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Microcrystalline cellulose</td>
<td>q.s.</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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</tr>
</tbody>
</table>

**Table 2: Evaluation of rapid disintegrating tablets**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Friability, % (n=6, ±SD)</th>
<th>Content uniformity, % (n=10, ±SD)</th>
<th>Drug content, % (n=6, ±SD)</th>
<th>Wetting time, sec (n=6, ±SD)</th>
<th>Hardness, Kg (n=6, ±SD)</th>
<th>Disintegration time, sec (n=6, ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.09±0.02</td>
<td>99.16±0.67</td>
<td>99.41±0.31</td>
<td>163±0.67</td>
<td>7.20±2.03</td>
<td>363±1.11</td>
</tr>
<tr>
<td>F2</td>
<td>0.11±0.01</td>
<td>99.31±0.79</td>
<td>99.23±0.32</td>
<td>192±0.93</td>
<td>7.80±2.94</td>
<td>398±2.14</td>
</tr>
<tr>
<td>F3</td>
<td>0.09±0.03</td>
<td>99.43±0.52</td>
<td>99.07±1.03</td>
<td>198±1.44</td>
<td>8.40±2.61</td>
<td>432±2.14</td>
</tr>
<tr>
<td>F4</td>
<td>0.07±0.03</td>
<td>99.99±0.17</td>
<td>99.34±0.33</td>
<td>159±1.03</td>
<td>6.80±1.33</td>
<td>317±2.11</td>
</tr>
<tr>
<td>F5</td>
<td>0.17±0.04</td>
<td>99.91±0.73</td>
<td>99.14±0.67</td>
<td>163±0.94</td>
<td>6.80±2.04</td>
<td>324±2.04</td>
</tr>
<tr>
<td>F6</td>
<td>0.13±0.02</td>
<td>99.47±0.57</td>
<td>99.16±0.67</td>
<td>178±1.33</td>
<td>7.10±1.47</td>
<td>331±1.73</td>
</tr>
<tr>
<td>F7</td>
<td>0.12±0.06</td>
<td>99.93±0.87</td>
<td>99.17±0.43</td>
<td>66.3±1.63</td>
<td>5.80±2.87</td>
<td>58.8±3.94</td>
</tr>
<tr>
<td>F8</td>
<td>0.21±0.08</td>
<td>99.91±0.74</td>
<td>99.84±0.67</td>
<td>57.0±1.33</td>
<td>5.70±3.25</td>
<td>47.0±2.34</td>
</tr>
<tr>
<td>F9</td>
<td>0.46±0.02</td>
<td>99.34±0.82</td>
<td>99.15±1.16</td>
<td>39.0±1.04</td>
<td>5.70±1.41</td>
<td>27.0±2.06</td>
</tr>
</tbody>
</table>

SD: Standard deviation
properties. Thus, we selected these materials as lubricants for this study. As the concentration of magnesium stearate and talc was increased up to 7% there is not much effect on the disintegration time. At the 12% lubricant concentration, the disintegration time of tablet containing magnesium stearate was found to be more than 55 Sec., whereas, tablets containing talc as a lubricant disintegrates in less than 40 Sec. The differences in the disintegration time of the tablets could be attributed to differences in the hydrophobic and hydrophilic properties of the two lubricants. Magnesium stearate is well known as a high hydrophobic lubricant, so that the oral disintegration time of tablets containing magnesium stearate is longer than tablets containing talc. The hydrophobic magnesium stearate film forms during blending will have a negative effect on the wettability of the tablet ingredient particles and hence retard water penetration into the tablets. However, if complete coating of lubricant is not formed during blending the lubricant film will not be perfect and water will enter the disintegrant particles and may decrease the disintegration time.

**Stability study**

According to ICH guidelines, selected formulation (F9) was stored at 40°C temperature and 75% relative humidity (RH) for a period of three months. Evaluation parameters studied did not show any major difference and all the values for disintegration test, wetting time, friability (%), hardness, drug content and content uniformity were found to be within acceptable limits.

**CONCLUSION**

The study conclusively demonstrated formulation and evaluation of fast disintegrating tablets of glipizide by using gum acacia, gum tragacanth and guar gum. Gum acacia and gum tragacanth showed insignificant disintegrant action because of gel forming nature. Glipizide tablets containing guar gum exhibited quick disintegration because when it comes in contact with water thereby generate enough pressure to initiate the disintegration well before the gel is formed.

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