Formulation and *in vitro* evaluation of theophylline anhydrous bioadhesive tablets

V N Deshmukh, J K Jadhav, D M Sakarkar

Department of Pharmaceutics, S N Institute of Pharmacy, Pusad, Dist. Yavatmal (MS), India

The aim of the current study was to design oral controlled release (CR) theophylline anhydrous bioadhesive tablets and to optimize the drug release profile and *in vitro* bioadhesion strength. Different types of natural hydrophilic polymers such as xanthan gum, locust bean gum, guar gum, karaya gum, and their combinations were used to formulate matrix tablets. Tablets of anhydrous theophylline were prepared by the direct compression method and were subjected to *in vitro* drug dissolution for 12 hours using the USP dissolution apparatus basket type at a speed of 100 rpm and temperature of 37 ± 0.5°C using gastric fluid (pH 1.2). The bioadhesive strength of the tablets was measured as the force of detachment against the porcine gastric mucosa. The *in vitro* release study as well as the retention time of the bioadhesive tablets on the mucous membrane were investigated to develop a bioadhesive polymer-based CR delivery system and to evaluate the performance of such a delivery device. The combination of karaya gum:guar gum (6:4) tablet showed a greater bioadhesive strength as compared with a single gum and other gum combination tablets. Karaya gum:guar gum-loaded tablets were not discharged from the mucous membrane and were dissolved in the gastric fluid. An increase in the gum concentration increases the drug release profile beyond 12 hours whereas there is no significant effect of gum concentration on the bioadhesive strength of the tablet.

**Key words:** Guar gum, karaya gum, locust bean gum, theophylline, xanthan gum

**INTRODUCTION**

Oral controlled release (CR) systems continue to be the most popular ones among all the drug delivery systems. Mucoadhesive delivery systems offer several advantages over other oral CR systems by virtue of prolongation of residence time of drug in the gastrointestinal tract, targeting, and localization of the dosage form at a specific site. Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs. Bioadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to a strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces and leads to adhesive interactions. Several studies reported bioadhesive oral drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes; however, very few reports on bioadhesive tablets using natural hydrophilic polymers are available. Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs. In our study, theophylline anhydrous is used as a model drug. The objective of this study is to develop, characterize, and evaluate mucoadhesive matrix tablets of theophylline employing various natural hydrophilic bioadhesive polymers such as xanthan gum, locust bean gum, gum karaya, and guar gum for prolonged gastrointestinal absorption. The prepared tablets were evaluated for different parameters such as swelling index, *in vitro* drug release rates, and *in vitro* mucoadhesive strength.

**MATERIALS AND METHODS**

Theophylline anhydrous was a kind gift from M/S. Lupin Pharmaceuticals Ltd., Aurangabad, India. Gum Karaya and Locust bean gum were gift samples from Krystal Colloids and Lucid Gums, Mumbai, India. Xanthan gum and Guar
gum were gift samples from Loba Chemie Pvt. Ltd., Mumbai, India. Lactose (direct compressible), magnesium stearate, and Aerosil were procured from Research Lab, Mumbai, India. For determining the bioadhesive strength, the porcine gastric mucosa was obtained from a local slaughter house. All other reagents employed were of analytical or pharmaceutical grade.

Preparation of the mucoadhesive tablet
A sustained release mucoadhesive oral tablet of theophylline was prepared by the direct compression method. In all the cases, the amount of the active ingredient is 100 mg. All the ingredients of the tablet were blended to obtain uniform mixing. Matrix tablets were prepared using a Cadmach single punch tablet machine (M/S Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India) using 8-mm flat surface punches. All the theophylline-loaded matrix tablets were stored in airtight containers at room temperature for further study. Tablets of Batch F1–F4 contain only single mucoadhesive polymer having a drug:gum ratio of 1:1, Batch F5–F7 contain combinations of various mucoadhesive polymers having a drug:gum ratio of 1:1, Batch F8–F11 contain only single mucoadhesive polymer having a drug:gum ratio of 1:0.5, and Batch F12–F14 contain combination of various mucoadhesive polymers having a drug:gum ratio of 1:0.5. Compositions of various formulations are shown in Table 1.

Evaluation of the mucoadhesive tablets
All the mucoadhesive tablets prepared were evaluated for the following official parameters: Hardness, Friability, Weight variation, Thickness, and Drug content as per official procedures. The values of all the evaluation parameters are shown in Table 2.

In vitro drug release study
The in vitro drug release studies of the matrix tablets were conducted in a USP type II dissolution apparatus equilibrated at temperature 37 ± 0.5°C and 100 rpm speed. The dissolution studies were carried out in triplicate for 12 hours in 900 ml of gastric fluid (pH 1.2). The dissolution samples were collected at every 1 hour interval and replaced with an equal volume of gastric fluid to maintain the volume constant. The sample solution was diluted sufficiently and analyzed at 272 nm as mentioned in USP and BP by a UV spectrophotometer (Shimadzu, Kyoto, Japan). The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from the reference standard of the respective drug. Drug dissolved at specified periods was plotted as a percent release versus time (hours) curve.

The in vitro release study of formulation F1–F14 is given in the plot of percentage cumulative drug release against time (hours), depicted in Figure 1.

Analytical method validation
The method was validated according to the International

Table 1: Composition of the mucoadhesive tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</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>
<th>F10</th>
<th>F11</th>
<th>F12</th>
<th>F13</th>
<th>F14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Karaya gum</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>70</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Guar gum</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>60</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>30</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Aerosil</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>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium stearate</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>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lactose (DC)</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2: Physical parameter of the mucoadhesive tablets

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Hardness (kg/cm²) mean ± SD</th>
<th>Friability (%) mean ± SD</th>
<th>Weight variation (mg) mean ± SD</th>
<th>Thickness (mm) mean ± SD</th>
<th>% drug content mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.92 ± 0.23</td>
<td>0.67</td>
<td>220 ± 0.44</td>
<td>4.92 ± 1.01</td>
<td>94.81 ± 0.68</td>
</tr>
<tr>
<td>F2</td>
<td>6.57 ± 0.52</td>
<td>0.62</td>
<td>220 ± 0.23</td>
<td>4.02 ± 0.56</td>
<td>96.72 ± 0.54</td>
</tr>
<tr>
<td>F3</td>
<td>7.02 ± 0.48</td>
<td>0.37</td>
<td>220 ± 0.85</td>
<td>4.90 ± 0.62</td>
<td>97.98 ± 0.84</td>
</tr>
<tr>
<td>F4</td>
<td>6.42 ± 0.41</td>
<td>0.66</td>
<td>220 ± 1.00</td>
<td>4.34 ± 0.48</td>
<td>92.18 ± 0.47</td>
</tr>
<tr>
<td>F5</td>
<td>6.63 ± 0.36</td>
<td>0.58</td>
<td>220 ± 0.64</td>
<td>4.08 ± 1.00</td>
<td>94.25 ± 0.72</td>
</tr>
<tr>
<td>F6</td>
<td>7.20 ± 0.57</td>
<td>0.38</td>
<td>220 ± 0.96</td>
<td>4.37 ± 0.68</td>
<td>96.80 ± 0.69</td>
</tr>
<tr>
<td>F7</td>
<td>6.67 ± 0.53</td>
<td>0.68</td>
<td>220 ± 1.00</td>
<td>4.12 ± 0.29</td>
<td>98.12 ± 0.83</td>
</tr>
<tr>
<td>F8</td>
<td>5.21 ± 0.71</td>
<td>0.59</td>
<td>220 ± 0.56</td>
<td>4.29 ± 0.43</td>
<td>94.43 ± 0.74</td>
</tr>
<tr>
<td>F9</td>
<td>6.33 ± 0.32</td>
<td>0.35</td>
<td>220 ± 0.63</td>
<td>4.68 ± 0.56</td>
<td>97.63 ± 0.68</td>
</tr>
<tr>
<td>F10</td>
<td>6.87 ± 0.42</td>
<td>0.42</td>
<td>220 ± 0.58</td>
<td>4.45 ± 0.83</td>
<td>98.92 ± 0.46</td>
</tr>
<tr>
<td>F11</td>
<td>7.00 ± 0.86</td>
<td>0.40</td>
<td>220 ± 0.47</td>
<td>4.28 ± 0.72</td>
<td>95.13 ± 0.83</td>
</tr>
<tr>
<td>F12</td>
<td>6.12 ± 0.77</td>
<td>0.51</td>
<td>220 ± 0.43</td>
<td>4.49 ± 0.79</td>
<td>92.68 ± 1.00</td>
</tr>
<tr>
<td>F13</td>
<td>6.13 ± 0.85</td>
<td>0.47</td>
<td>220 ± 0.68</td>
<td>3.39 ± 0.62</td>
<td>98.89 ± 0.56</td>
</tr>
<tr>
<td>F14</td>
<td>6.17 ± 0.75</td>
<td>0.45</td>
<td>220 ± 0.41</td>
<td>3.27 ± 0.47</td>
<td>96.68 ± 1.00</td>
</tr>
</tbody>
</table>
Conference of Harmonization guidelines for validation of analytical procedures.[13] The validation parameters were accuracy and precision. The accuracy and precision were investigated at three concentration levels of theophylline with six independent replicates on the same day and on six consecutive days. The intraday and interday bias values were found to be less than 1.65% and 1.12% and the intraday and interday relative standard deviation values were less than 2.16% and 1.84%, respectively.

In vitro mucoadhesive study[14-17]

The mucoadhesive strength of the tablets was measured on a modified physical balance [Figure 2]. The apparatus consist of a modified double beam physical balance in which the right and the left pan have been replaced by lighter pans. The left side of the balance was made 5 g heavier than the right side by placing a 5 g weight on left side pan. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker, which was then placed below the left hand set of the balance.

The porcine gastric mucus membrane was used as the model membrane and pH 1.2 solution was used as the moistening fluid. The porcine stomach mucosa[18,19] was kept in Tyrode solution at 37°C for 2 hours. The underlying mucus membrane was separated and washed thoroughly with a pH 1.2 solution. It was then tied to a Teflon-coated glass slide and this slide was fixed over the protrusion in the Teflon block using a thread. The block was then kept in a beaker containing pH 1.2 buffer solution at the level that just touches the membrane so as to moisten the membrane. By keeping a 5 g weight on the right pan, the two sides of the balance were made equal. The beaker with the Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the left hand side pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with a weight of 5 g. This was kept undisturbed for 3 minutes. Then, the weight on the right hand side was slowly added in an increment of 0.5 g till the tablet just separated from the membrane surface. The excess weight on the right pan i.e., total weight minus 5 g was taken as a measure of the mucoadhesive strength. From the mucoadhesive strength, the force of adhesion was calculated using the following formula:

\[
\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \times 9.81
\]

Results are summarized in Table 3.

Stability study

Stability study was carried out on the optimized formulation F13. The tablets of formulation F13 were first wrapped in an aluminum foil and then placed in an amber-colored bottle. This was stored at 40 ± 2°C and 75 ± 6% relative humidity for 6 months. The tablets were evaluated for mucoadhesive properties and in vitro drug release after 2, 4, and 6 months.[20]

![Figure 1: Percent cumulative drug release of formulation F1–F14](image-url)
Results obtained were compared with the data obtained for zero time at room temperature and humidity (temperature 28 ± 2°C and humidity 42 ± 2%).

The results of the in vitro release study of formulation F13 after the stability study are shown in Table 1 and the plot of comparative release is shown in Figure 3.

RESULT AND DISCUSSION

All the batches were evaluated for the physical properties and hardness of the tablet in the range of 6–7 kg/cm². Percentage weight loss in the friability test was less than 0.7% in all the batches and all the batches contained Theophylline within 100 ± 5% of the labeled content. Overall, the prepared tablet batches were of good quality with regard to hardness, friability, and drug content.

The in vitro mucoadhesive strength study was performed on the modified physical balance to measure the force (N) required for detaching the tablet. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers [Table 3]. Viscosity of the polymer also affects the bioadhesive strength of the tablet.

From the overall dissolution profiles, it was concluded that the drug release rate decreased as the concentration of the polymer increased, which was also affected by the type of polymer used. This can probably be attributed to the different diffusion and swelling behaviors of the polymers.

The stability study showed that there was no change in the appearance and on drug release pattern of the tablets.

From the results of the dissolution data, the Korsmeyer and Peppas model was found to be best fitted in all dissolution profiles having a higher correlation coefficient. Thus, it was concluded that the drug release occurred via a diffusion mechanism and due to the affinity of natural hydrophilic polymers toward water, there is bioadhesiveness of the natural hydrophilic polymers.

CONCLUSION

Review of the literature indicates that gastroretentive drug delivery systems can be used to increase the gastric residence time of dosage form, which led to an increased bioavailability of various drugs.

Thus, in the present investigation, an attempt was made to deliver Theophylline via an oral mucoadhesive drug delivery system to the vicinity of the absorption site by prolonging the gastric residence time of the dosage form. For the formulation of the oral mucoadhesive tablet, various hydrophilic polymers and their combinations were used in varying concentrations.
Tablets were subject to various evaluation parameters such as Hardness, Friability, Drug content, Mucoadhesive strength study, and in vitro drug release study. It was revealed that tablets of all batches had acceptable physical parameters. Tablets of batch F13 have good mucoadhesion along with in vitro drug release. It was observed that tablets of all batches followed the equation of Korsmeyer and Peppas drug release profiles. Tablets of Batch F13 were selected as an optimum batch.

Stability studies revealed that there was no significant change in the hardness, friability, drug content, and dissolution profile of formulation F13. Thus, this formulation was stable at different conditions of temperature.

The present study shows that the hydrophilic gums obtained from natural sources can be used for designing a mucosahcesive CR drug delivery system.

REFERENCES