Independent release behavior of Glipizide matrix release tablets containing chitosan and xanthan gum

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Abstract
The aim of this study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of Glipizide (G) from matrix tablets containing chitosan and xanthan gum prepared by a hot-melt extrusion process. The release mechanisms were controlled by the solubility and ionic properties of the polymers. All directly compressed (DC) tablets prepared in this study also exhibited pH and buffer species dependent release. In contrast, the HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release. When placed in 0.1N HCl, the HME tablets formed a hydrogel that functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained high ionic strength, whereas tablets without chitosan did not form a hydrogel to retard drug release in 0.1N HCl.

Keywords: Chitosan; Xanthan gum; Direct compression; Hot-melt extrusion; Sustained release; Hydrogel; pH independent release

INTRODUCTION
The pH of the gastrointestinal tract (GI tract) varies from pH 1 to 3 in the stomach and increases to approximately pH 7–8 in the colon. Furthermore, the pH of the stomach can fluctuate with food intake, as well as with the age and health of the patient. Sustained release dosage forms extend the duration time of drug therapy, reduce side-effects and increase safety and patient compliance by reducing the frequency of dosing. Multiple daily administration of an immediate release dosage form results in patient non-compliance. To control and modulate drug release properties of tablets, retardant polymers including hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sodium alginate and polyvinyl alcohol (PVA) as well as the ammonio methacrylate copolymers such as Eudragit RL and RS, or methacrylic acid copolymers like Eudragit L and S, have been utilized in solid dosage forms. For these retardants, hydrophilic polymers control drug release from tablets by hydrogelation. The retardation mechanism is based on the intramolecular hydrogelation of a hydrophilic polymer during dissolution and has been reported to be affected by the ionic strength of the dissolution medium. Due to differences in ionic strength of gastric and intestinal fluids, as well as wide variations and fluctuations in its pH of the GI tract, the in vitro and in vivo data for sustained release dosage forms may not always correlate.

The aim of our study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of Glipizide from matrix tablets containing hydrophilic retardant polymers prepared by a hot-melt extrusion process. Chitosan and xanthan gum were investigated as the model hydrophilic retardant polymer. Chitosan is a linear hydrophilic polysaccharide polymer of d-glucosamine. It is a non-toxic natural polycationic polymer that is degraded by the microflora in the colon. Chitosan is produced by the alkaline deacetylation of chitin. It is an abundant polymer in nature and is present in the exoskeleton of crustaceans such as crabs or shrimp. Chitosan has been widely researched for its potential use as a pharmaceutical ingredient. The characteristics of cross linked chitosan with an anionic polymer, applications of chitosan in controlled release dosage forms, evaluations of matrix tablets containing microcrystalline chitosan and applications of chitosan in thermo-sensitive chitosan based hydrogels have been reported. In addition, the ability of chitosan to retard drug release depends on its molecular weight. High molecular weight chitosans function as matrix tablet retardants, whereas low molecular weight chitosans can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wet ability resulting from the solubility of low molecular weight chitosans in water (less than 10,000). Xanthan gum is a polysaccharide consisting of a cellulose backbone and trisaccharide side chains containing glucuronic acids that give this polymer a negative charge. Although primarily used as a suspending agent, xanthan gum has been reported to function as a matrix retardant in solid dosage forms.
Materials and methods

Materials

Chitosan and Glipizide were gift samples from Aurobindo Pharma Pvt. Ltd. PEO, Xanthan gum and microcrystalline cellulose were purchased from Loba Chemie Pvt Ltd (Mumbai, India). Glipizide was passed through a 150# screen prior to further processing.

Preparation of directly compressed (DC) tablets

A 200 g sample of powder containing 10% Glipizide as the model drug, functional polymers and excipients were blended using a mortar and pestle for 2 min. A 300 mg sample of the blended materials was then compressed using a hydraulic compactor at the pressure of 2000 kg. The hardness of a DC tablet was measured in six replicates using a Monsanto tablet hardness tester.

Preparation of hot-melt extruded (HME) tablets

The formulations used in this study are shown in Table 1. A 200g sample of powder containing 10% Glipizide, functional polymers and excipients was first blended in a mortar and pestle for 2 min. The blended materials were then fed into the hopper of a single screw Randcastle extruder. The processing temperatures were 90°C (zone 1), 95°C (zone 2), 105°C (zone 3) and 110°C (die). The screw speed was 15 rpm and the processing time for the powders inside the barrel of the extruder was approximately 3–4 min. The extruded materials were stored at room temperature for at least 48 h and manually cut into tablets weighing approximately 300 mg.

Fourier transform infrared (FT-IR)

Fourier transform infrared (FT-IR) spectral studies were conducted on FTIR Spectrophotometer (Shimadzu Instrument Corporation Inc., Japan) instrument using KBr pellets to investigate possible interactions between the respective polymers in the release media. All samples were crushed with potassium bromide. The weight ratio of a sample and potassium bromide was 2 mg to 300 mg. Crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 min. FT-IR measurements were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm⁻¹ at a resolution of 4 cm⁻¹.

In vitro drug release

In vitro release testing of tablets (300 mg) containing 10 mg Glipizide was carried out in the USP 27 Apparatus 2 Dissolution tester. The dissolution medium was 900 ml of either 0.1N HCl, pH 4.0 acetate buffers (100 mM), pH 4.0 citrate buffers (100 mM), PH 4.0 phosphate buffer (100 mM), pH 6.8 phosphate buffers (50 mM) or pH 7.4 phosphate buffers (50 mM). To evaluate the influence of ionic strength on Glipizide release from matrix tablets, 0.1N HCl, pH 4.0 acetate buffers, pH 6.8 phosphate buffers and pH 7.4 phosphates buffer each containing 0.4M NaCl were prepared. During dissolution testing, the media were maintained at 37±0.5°C and agitated at 100 rpm. A sample volume of 3ml was taken at each sampling time point. All dissolution tests were conducted for 12 hrs. Samples were analyzed using a UV spectrometer (Elico instruments, hyd, India) at 276 nm. All dissolution tests were performed in triplicate. The experimental results were fitted to the following exponential equation proposed by Ritger and Peppas²⁴.

\[ M_t / M_\infty = k t^n \]

Where, \( M_t \) is the amount of drug released at time \( t \), \( M_\infty \) is the amount of drug released at infinity, and \( k \) is a dissolution rate constant and \( n \) is the diffusional exponent characteristic of the release mechanism. The values of \( n \) were obtained by regression analysis. In the case of drug release from a swellable cylindrical device such as HME tablets containing hydrophilic polymers, the exponent \( n \) of Fickian diffusion is defined by \( n = 0.45 \), whereas anomalous (non-Fickian) transport is \( 0.45<n<0.89 \) and Case-II transport is indicated by \( n = 0.89 \) (Ritger and Peppas⁴⁰).

Results and discussion

In vitro drug release studies

Glipizide release from DC tablets

All formulations in Table 1 were used to investigate the Glipizide release properties from DC tablets. The hardness of DC tablets prepared from formulations 2 and 3 were both over 16 kg. They exhibited pH and buffer species dependent release. In Figure 3, the Glipizide release rate in 0.1N HCl from DC tablets containing both chitosan and xanthan gum was faster than in other media. Almost 100% Glipizide released from DC tablets within 8hr in 0.1N HCl, suggesting that the hydrogel formed in 0.1N HCl during dissolution testing as a retardant mechanism did not function to retard drug release for 12 hrs.
Figure 1. Glipizide release profiles from DC tablets prepared by formulations

Table 1. Tablet formulations used in the present study.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation 1</th>
<th>Formulation 2</th>
<th>Formulation 3</th>
<th>Formulation 4</th>
<th>Formulation 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Chitosan</td>
<td>51</td>
<td>-</td>
<td>17</td>
<td>23</td>
<td>09</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>09</td>
<td>23</td>
<td>26</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>-</td>
<td>37</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>PEO</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>GMS</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Glipizide release from HME tablets

The Glipizide release profiles of HME tablets prepared from formulation 1 containing chitosan exhibited both pH and buffer species dependent release (Figure 2). The Glipizide release rates in 0.1N HCl and pH 4.0 acetate buffer were slower than in other media. These results could be explained by both the solubility of chitosan and the difference in hydrogelation rate of chitosan in the respective dissolution media. Gelation of chitosan was visually observed during dissolution testing in 0.1N HCl and pH 4.0 acetate buffer, whereas no distinct hydrogel formulation in other media was observed. Highly deacetylated chitosan is soluble up to a pH of 6.5 therefore, retardation of drug release by intramolecular hydrogel formation occurred in 0.1N HCl and pH 4.0 acetate buffers, but not in pH 6.8 and 7.4 phosphate buffers. In pH 4.0 buffers, the Glipizide release rate from HME tablets prepared from formulation 1 was buffer species dependent. This could be explained by the difference in the solubility of chitosan in dilute acids. Chitosan is soluble in dilute acetic acid and HCl, while it is slightly soluble in dilute H₃PO₄ and is partially soluble in dilute citric acid. When the medium can dissolve chitosan completely, the solution will show a high viscosity.
The Glipizide release rates from HME tablets prepared by formulation 2 containing xanthan gum were also pH dependent (Figure 3) and were similar to those from DC tablets (data not shown). In 0.1N HCl, Glipizide release was especially rapid due to the difference in the ionization state of xanthan gum in the dissolution media. In general, xanthan gum is present predominantly in a unionized state at low pH, whereas xanthan gum is ionized under dilute acidic and alkaline conditions. This difference in the ionization state of xanthan gum in the dissolution media affected hydrogel formation and consequently, the retardation of drug release. When xanthan gum was present in an unionized state, an intramolecular hydrogelation was prevented due to the absence of ionic bonds, resulting in a rapid release of Glipizide in 0.1N HCl, phosphate buffer pH 7.4 at 37° ± 0.5°C represents the mean ± S.D., n =3.

Interestingly, Glipizide release from HME tablets containing both chitosan and xanthan gum (formulation 3) showed pH and buffer species independent sustained release (Figure 4), while Glipizide release from DC tablets exhibited pH and buffer species dependent release (Figure 1).

In pH 4.0 acetate buffer, Glipizide release rates from HME and DC tablets were almost the same, whereas in 0.1N HCl, the Glipizide release rate from DC tablets was faster than that from HME tablets. This could be attributed to the difference in media uptake speed into HME and DC tablets during dissolution test. The major difference between HME and DC tablets prepared in this study was the PEO state in the tablet. In the DC tablets, PEO is dispersed as a powder, whereas the PEO in HME tablets was present as a melt due to the melting which occurred during the hot-melt extrusion process. The media uptake speed into a DC tablet was faster than that for the HME tablet. This was visually observed in the cross sectional morphologies of freeze-dried HME and DC tablets extracted from vessels after 6 h during a dissolution test. The penetration rate (P) of media into a tablet was calculated by the following equation:

$$P (%) = \frac{m}{d} \times 100$$

Where, m is the penetrated distance of 0.1N HCl from surface to center of tablets and d is the radius of tablets. The penetration of 0.1N HCl into HME tablets in 6 h was approximately 72%, whereas that into DC tablets was
100%, suggesting the media uptake speed for DC tablets was faster than HME tablets. This difference in media uptake speed into HME and DC tablets would affect the drug release rate from a tablet via a hydrogel of chitosan formed in 0.1N HCl since an intra-molecular hydrogel of chitosan could be sensitive due to the low viscosity property, resulting in the fast drug release in 0.1N HCl from a DC tablet. In order to evaluate the release mechanism from a HME tablet, the Glipizide dissolution data up to 60% was taken and a linear fit was generated by a double logarithmic plot. The diffusional exponent (n), correlation coefficient (r²) and dissolution rate constant (k) values are shown in Table 2. The Glipizide release profile from HME tablets prepared according to formulation 3 in the dissolution media without 0.4 M NaCl followed an anomalous (non-Fickian) drug release with the exception of pH 4.0 acetate buffer. Drug release in pH 4.0 acetate buffer was close to Case-II transport, suggesting that the Glipizide release is controlled mainly by hydrogel matrix formation during dissolution, rather than by drug diffusion.

Table 2. Drug release kinetics from HME tablets.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Medium</th>
<th>0.4 M NaCl</th>
<th>n ± S.D.</th>
<th>r²</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation 1</td>
<td>0.1N HCl</td>
<td>Without</td>
<td>0.680 ± 0.019</td>
<td>0.999</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>0.1N HCl</td>
<td>With</td>
<td>0.633 ± 0.026</td>
<td>0.9985</td>
<td>21.1</td>
</tr>
<tr>
<td>Formulation 2</td>
<td>pH 4.0 acetate</td>
<td>Without</td>
<td>0.676 ± 0.018</td>
<td>0.9994</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>pH 7.4 phosphate</td>
<td>Without</td>
<td>0.646 ± 0.012</td>
<td>0.9996</td>
<td>16.7</td>
</tr>
<tr>
<td>Formulation 3</td>
<td>0.1N HCl</td>
<td>Without</td>
<td>0.721 ± 0.012</td>
<td>0.9999</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>0.1N HCl</td>
<td>With</td>
<td>0.655 ± 0.014</td>
<td>0.9995</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>pH 4.0 acetate</td>
<td>Without</td>
<td>0.836 ± 0.006</td>
<td>0.9998</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>pH 4.0 acetate</td>
<td>With</td>
<td>0.698 ± 0.007</td>
<td>0.9999</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>pH 4.0 citrate</td>
<td>Without</td>
<td>0.702 ± 0.025</td>
<td>0.9997</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>pH 4.0 phosphate</td>
<td>Without</td>
<td>0.728 ± 0.010</td>
<td>0.9998</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>pH 6.8 phosphate</td>
<td>Without</td>
<td>0.691 ± 0.008</td>
<td>0.9999</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>pH 7.4 phosphate</td>
<td>Without</td>
<td>0.649 ± 0.013</td>
<td>0.9998</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>pH 7.4 phosphate</td>
<td>With</td>
<td>0.715 ± 0.010</td>
<td>0.9904</td>
<td>30</td>
</tr>
</tbody>
</table>

Effect of ionic strength on Glipizide release

To investigate the influence of ionic strength on Glipizide release, dissolution testing of the HME tablets prepared according to formulations 2 and 3 in 0.1N HCl, pH 4.0 acetate buffer and pH 7.4 phosphate buffer each containing 0.4 M NaCl was. The Glipizide release rates in pH 4.0 acetate buffer containing 0.4 M NaCl and pH 7.4 phosphate buffer containing 0.4 M NaCl from HME tablets prepared by formulation 2 containing xanthan gum were significantly faster than those without 0.4 M NaCl. These phenomena are due to the polymer configuration change of xanthan gum. The Glipizide release profiles of HME tablets prepared from formulation 3 were not affected by an increase in the ionic strength of 0.1N HCl and pH 4.0 acetate buffers. This result demonstrated that the retardation mechanism in acidic media of HME tablets containing both chitosan and xanthan gum was not affected by the xanthan gum polymer. However, the Glipizide release rate from HME tablets prepared from formulation 3 in pH 7.4 phosphate buffer containing 0.4 M NaCl was much faster than that in pH 7.4 phosphate buffer. This can be explained by the solubility of chitosan and the polymer configuration change of xanthan gum caused by an increase in the ionic strength of the dissolution medium. The intermolecular hydrogelation between chitosan and xanthan gum did not occur since highly deacetylated chitosan was insoluble at a pH above 6.5. In addition, the intra-molecular hydrogelation of xanthan gum did not occur by the polymer configuration change with an increase of the ionic strength in dissolution medium.

Moreover, the influence of the ionic strength on the Glipizide release mechanism was evaluated in terms of pharmaceutical kinetics. The n, r² and k values are shown in Table 2. When 0.4 M NaCl was present in the dissolution media, the diffusional exponent value changed slightly toward the value (n = 0.45) of a Fickian diffusion, and the dissolution rate constant increased. This could be due to the prevention of hydrogelation of xanthan gum according to an increase in the ionic strength of the dissolution medium.

In vitro drug release on media replacement

To investigate the drug release properties from HME tablets under the variable pH environments, the dissolution medium were replaced every 3 h. The 0.1N HCl was used as the first medium, then the medium was replaced.
with pH 4.0 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer, continuously. Furthermore, to investigate the influence of ionic strength on Glipizide release, dissolution media containing 0.4 M NaCl were also used in this study.

In the drug release profiles in 0.1N HCl, the averages of Glipizide release in 6 and 10 h of HME tablets prepared from formulation 1 containing chitosan were 70.2% and 98.9%, respectively. On the other hand, those of HME tablets prepared from formulation 3 containing both chitosan and xanthan gum were 60.3% and 85.9%, respectively. The Glipizide release rate from HME tablets prepared from formulation 3 was slower than formulation 1. These results suggested that the retardation mechanism in 0.1N HCl is a function of both an intra-molecular hydrogel of chitosan and an inter-molecular hydrogel between chitosan and xanthan gum, although the main retardation mechanism was due to an intra-molecular hydrogel formed by chitosan.

Table 3. Retardation mechanism in dissolution media of Glipizide from HME tablets prepared from formulation 3

<table>
<thead>
<tr>
<th>Dissolution media</th>
<th>In each medium</th>
<th>Media replacement study</th>
<th>Ionization state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without 0.4M NaCl</td>
<td>With 0.4M NaCl</td>
<td>Without 0.4M NaCl</td>
</tr>
<tr>
<td>0.1N HCl</td>
<td>A, C</td>
<td>A, C</td>
<td>A, C</td>
</tr>
<tr>
<td>pH 4.0 acetate</td>
<td>A, H, C</td>
<td>rapid release</td>
<td>A, C</td>
</tr>
<tr>
<td>pH 6.8 phosphate</td>
<td>rapid release</td>
<td>A, C</td>
<td>A, C</td>
</tr>
<tr>
<td>pH 7.4 phosphate</td>
<td>rapid release</td>
<td>A, C</td>
<td>A, C</td>
</tr>
</tbody>
</table>

In pH 4.0 acetate buffer, the dissolution profiles of HME tablets prepared from formulations 1–3 were all similar. When 0.4 M NaCl was present in pH 4.0 acetate buffer, the dissolution profile of HME tablets prepared from formulations 1 (data not shown) and 3 were unchanged, whereas that of HME tablets prepared from formulation 2 containing xanthan gum was affected by an increase in the ionic strength of media. These results indicate that the retardation mechanism in pH 4.0 acetate buffer was according to the intra-molecular hydrogelation of chitosan itself and/or the inter-molecular hydrogelation between chitosan and xanthan gum. In the case of pH 4.0 citrate and phosphate buffers, the retardation mechanisms were mainly according to inter-molecular hydrogelation between chitosan and xanthan gum, because the Glipizide release rates in pH 4.0 citrate and pH 4.0 phosphate buffers from HME tablets prepared from formulation 1 containing chitosan were rapid, whereas the release profiles of HME tablets prepared from formulation 3 containing both chitosan and xanthan gum showed sustained release and the Glipizide release properties were not affected by the ionic strength (data not shown).

A: intra-molecular hydrogelation of chitosan;
B: intra-molecular hydrogelation of xanthan gum;
C: inter-molecular hydrogelation between chitosan and xanthan gum.

These results suggested that the retardation mechanism in pH 4.0 citrate and phosphate buffers of HME tablets prepared from formulation 3 occurred primarily by the inter-molecular hydrogelation between chitosan and xanthan gum. The Glipizide release profiles in pH 6.8 and 7.4 phosphate buffers of HME tablets prepared from formulation 3 were controlled by only an intra-molecular hydrogelation of xanthan gum because chitosan is insoluble at a pH above 6.5. In fact, when 0.4 M NaCl was present in pH 6.8 phosphate buffer (data not shown) and pH 7.4 phosphate buffer, the Glipizide release rates were significantly faster due to the polymer configuration change of xanthan gum.

Conclusion

Glipizide release from HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release attributable to the combination of the property of slow media uptake speed into a tablet due to the melt state of PEO by a hot-melt extrusion process, the intra-molecular hydrogelation properties of chitosan at a pH below 6.5, the intra-molecular hydrogelation properties of xanthan gum at pH 4.0, 6.8 and 7.4, and the inter-molecular hydrogelation properties of chitosan and xanthan gum under acidic conditions. In acidic media, the sustained release property of the HME tablets containing both chitosan and xanthan gum was not affected by the ionic strength in media. Furthermore, in a media replacement study, the hydrogel that was formed in acidic media functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained 0.4 M NaCl.

It is proposed that the pH and buffer species independent sustained release HME tablet may exhibit the same release profile in the GI tract since a hydrogel is formed in acidic media similar to stomach fluid, and the resulting hydrogel would function to retard drug release in neutral and slightly alkaline media, irrespective of ionic strength.
References


