Guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics

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Abstract

The effect of ionic and non-ionic excipients and additives as modulators of swelling and erosion kinetics and verapamil HCl release from guar-based matrix tablets was investigated. Tablet dissolution, erosion and water uptake studies were carried out using a modified USP 23 Apparatus 2 method. The kinetics of gel strength and texture development were studied by textural analysis. Near linear drug release over 24 h was obtained from formulations containing water soluble, ionizable sodium chloride and glycine. The contribution of Fickian release to overall drug release was lowest for these formulations and was correlated with greater gel strength and lower water uptake in the early time period. For soluble sugars (lactose and sucrose) the Fickian contribution to overall drug release was large and associated with pronounced curvilinear profiles. Water uptake was greatest for these additives (450% in 6 h). The lowest water uptake and negligible matrix erosion was observed for microcrystalline cellulose. Release from this formulation was predominantly Fickian. It was found that the physico-chemical nature of added excipients significantly influences the release kinetics from guar-based formulations. Ionic, water soluble materials (sodium chloride, glycine) reduce initial hydration of the matrix and thus have the ability to limit the initial rapid diffusion of drug and to sustain near linear release over 24 h. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Guar gum; Ionic and non-ionic excipients; Interaction; Release kinetics; Gel dynamics

1. Introduction

In recent years the value of hydrophilic polymer-based matrix tablets as vehicles for controlled release delivery has been increasingly demonstrated with the publication of numerous patents and research papers and their utilization in new products in the market place. In part the widespread and successful use of such polymeric systems can be attributed to their ease of manufacturing, relatively low cost, their favorable in vivo performance and their versatility in controlling the release of drugs with a wide range of physicochemical properties.

In particular, water-soluble cellulose ethers (e.g. hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC)) have been intensively...
studied for this application [1–5]. Other hydrophilic polymers also find frequent use, including polyethyleneoxide (PEO), polyvinyl alcohols, carbopol and numerous polysaccharides such as xanthan gum, chitosan, alginic acid, pectin and guar gum.

Recently the potential of guar gum on its own as an inexpensive and flexible carrier for oral extended release drug delivery has been highlighted. In vitro and in vivo release of a highly soluble drug (diltiazem) from guar matrix tablets was found to be similar to that of a commercial reference product (Dilacor XR®) [6]. It was also found that the guar formulations were relatively insensitive to changes in stirring speed during in vitro dissolution testing and that the dissolution profiles were not significantly affected by changes in compaction pressure or by storage under accelerated stress conditions. The same group of scientists has also shown that in vitro/in vivo correlations can be successfully established for guar-based systems [7]. Furthermore guar-based formulations for low solubility drugs (ketoprofen and nifedipine) with comparable release to commercial products (Oruvail® and Procardia XL®) were also developed [8,9].

However, little is known about the effect of excipients and additives on drug release from guar-based matrix tablets. This is of particular importance as the inclusion of various additives (ranging from sugars to salts and other polymers) in polymeric matrix systems can be utilized to affect matrix swelling, erosion and/or solubility of the drug and thus to modulate release kinetics.

Examples of this include the use of soluble diluents such as lactose to serve as erosion promoters in combination with swelling matrix formers such as HPMC [10]. Also sodium carboxymethylcellulose (NaCMC), which tends to promote matrix erosion and breakup of HPMC matrices, has been shown to retard the release of tertiary amines such as chlorpheniramine and various β-blockers (exprorenol, propranolol, metoprolol). This has been attributed to the ionic interaction between the amine groups of the drug molecules and the carboxyl groups of the cellulose [11,12]. In selected cases added excipients may also promote polymer cross-linking as is the case with alginates and pectins in the presence of calcium-ion-containing diluents such as dicalcium phosphate [13]. Cross-linking has also been found to be the basis for the synergistic increase in viscosity of the heterogeneous gel observed when locust bean gum is combined with xanthan gum [14,15]. Highly hydrophilic excipients such as electrolytes and sugars have also been documented to interact with polymeric carriers by causing a partial dehydration and ‘salting out’ of the polymer molecules [16]. Addition of inorganic salts such as sodium chloride has been shown to lower the gel point and increase the gel strength of HPMC [17]. Recently it was shown that inclusion of inorganic salts in simple HPMC and PEO matrices can result in zero order release of water soluble drugs such as diltiazem [18,19].

In order to further assess the potential usefulness of guar as an extended release excipient, the effect of a series of common pharmaceutical additives (with diverse physicochemical properties) on the swelling, erosion and drug release of a guar-based verapamil formulation was investigated. Verapamil HCl was chosen as a model water soluble drug that is frequently formulated in moderately high drug loadings (typical daily dose 240–360 mg/day).

2. Materials and methods

2.1. Materials

Verapamil HCl USP was obtained from Orion (Kupio, Finland). Guar gum NF (Supercol G3 and Supercol U) was a gift from Aqualon, Division of Hercules (Wilmington, DE). The additives/fillers that were used included: sucrose NF, sodium chloride USP, citric acid USP, sodium bicarbonate USP (all from Fischer Scientific, Fairlawn, NJ), lactose anhydrous NF (Sheffield, Norwalk, CT), microcrystalline cellulose NF (Avicel pH101, FMC Corp., Philadelphia, PA), dicalcium phosphate NF (Emcompress, E. Mendel, NY) and glycine USP (Sigma, St. Louis, MO). Magnesium stearate NF (Malinckrodt, St. Louis, MO) was used as a lubricant.

2.2. Preparation of matrix tablets

Verapamil HCl USP (40% of final mix), guar gum NF (Supercol G3, 18% of final mix) and the relevant additive/filler (18% of final mix) were wet massed in
a planetary mixer (Kitchen Aid) by adding a sufficient quantity of water. The wet mixture was then passed through a 1-mm stainless steel sieve mounted on an oscillating granulator (Erweka, Heusenstamm, Germany) and dried under vacuum at 50 °C for 3 h. After de-aggregation (1 mm sieve), an extragranular fraction of guar gum (Supercol U, 24% of the final mix) was added to the granules by dry blending for 10 min in a V-mixer (Patterson-Kelly, East Stroudsburg, PA). A constant amount of granulate (600 mg) was then compressed on a hydraulic press (Fred S. Carver, Wabash, IN) using a matching flat round 11-mm pre-lubricated punch and die set at a force of 15 kN which was maintained for ~10 s.

2.3. Dissolution testing

Tablet dissolution was assessed using standard USP 23 Apparatus II (paddle) equipment (Vankel, Cary, NC). To avoid the adhesion of the sticky, hydrating tablets to the bottom of the dissolution vessel, the apparatus was modified by the inclusion of stainless steel ring mesh devices in each flask as previously described [20]. A stirring speed of 50 rev./min was used to agitate the dissolution medium which was kept at 37 °C throughout and consisted of 1000 ml of pH 1.5 USP buffer. The drug concentration was determined automatically every 30 min by UV spectrophotometry at 230 nm (diode array spectrophotometer, HP 8452A and a six-channel peristaltic pump, Hewlett Packard, Wilmington, DE).

2.4. Mass loss and water uptake studies

Erosion and water uptake of the tableted formulations was determined under conditions identical to those described above for dissolution testing. Water uptake and mass loss were determined gravimetrically according to the following equations:

\[
\% \text{ water uptake} = 100 \times \frac{\text{remaining dry weight} - \text{wet weight}}{\text{remaining dry weight}} \tag{1}
\]

\[
\% \text{ mass loss} = 100 \times \frac{\text{remaining dry weight}}{\text{original dry weight}} \tag{2}
\]

Three tablets were used per time point. At the predetermined times the ring mesh assemblies supporting the partially hydrated tablets were carefully removed and the tablets were lightly patted with tissue paper to remove excess surface water. After determining the wet weight the tablets were dried at 70 °C for 10 days, before reweighing to determine the remaining dry weight. Placebo tablets consisting of pure polymer were treated in the same way.

2.5. Textural analysis of swelling behavior

To further investigate the swelling behavior of the various formulations, the cylindrical surface area and one planar face of each compact was coated with an organic water resistant coating (Eudragit RS in acetone–isopropanol) and affixed to a petri dish which was then placed in the dissolution vessel filled with dissolution medium at 37 °C. A paddle speed of 50 rev./min was used to simulate the tablet dissolution process. The partially hydrated samples were removed at predetermined intervals and subjected to textural profiling to determine gel layer thicknesses and movement of the water penetration front. Textural analysis was performed using a TA.XT2 Texture Analyzer equipped with a 5 kg load cell and Texture Expert software (Texture Technologies Corp, Scarsdale, NY/ Stable Micro Systems, Goldalming, UK). The force–displacement–time profiles associated with the penetration of a 2-mm round, flat-tipped steel probe into the swollen matrices were monitored at a data acquisition rate of 200 points per second. Once a trigger force of 0.005 N was detected, the probe was advanced into the sample at a test speed of 0.1 mm/s until the maximum force of 39.227 N (4000 g) was reached. This force had earlier been shown to be sufficient to penetrate into the unswollen glassy core. All measurements were carried out in triplicate.

2.6. Data analysis

The various models describing drug release were fit to the dissolution data using linear and non-linear regression analysis (Sigma Plot vs. 2. Jandel Scientific). Comparisons amongst multiple means were made by one-way analysis of variance followed by Tukey’s test and the Newman–Keuls test at the 95%
level of confidence [21] (Statgraphics vs. 5.0, Statistical Graphics Corporation).

3. Results and discussion

3.1. Release characterization

Drug release from swellable water soluble polymer systems is typically described in terms of two simultaneously operating mechanisms. These are Fickian diffusion through the hydrated outer layers of the matrix and matrix relaxation/erosion [22,23]. The contributions of these two mechanisms to the overall release are considered additive. A well-known empirical model that describes these phenomena is that of Peppas and Sahlin [24]:

\[ Q = k_1 t^m + k_2 t^{2m} \]  

(3)

where \( Q \) represents the drug fraction released in time, \( t \), \( (Q \leq 60\%) \), \( k_1 \) and \( k_2 \) represent kinetic constants associated with diffusional and relaxational release, respectively, and \( m \) is the purely Fickian diffusion exponent. Depending on the aspect ratio of the device, \( m \) varies between 0.43 and 0.5. The purely diffusional component was determined by fitting the release data to the following diffusion equation as recently described [3]:

\[ \% \text{ Released} = k t^{0.43} + c \]  

(4)

where \( k \) is the diffusional rate constant (units h\(^{-0.43}\)) and \( c \) is a constant. While release from tablets is frequently described in terms of the square root of time \( (m = 0.5) \), this is not appropriate in this case as the aspect ratio \( (\text{diameter}/\text{height}) \) of the tablets varies between 1.9 and 2.3. Based on the previously published data of Peppas and Sahlin [24], \( m = 0.43 \) is more appropriate for this geometry. The region of the profile where release is linear with \( t^{0.43} \) was identified by linear regression based on maximizing the correlation coefficient and achieving a random residual plot. It is assumed that the linear portion of the plot represents the duration over which diffusion predominates and that this apparent diffusion rate can be used to approximate the diffusional contributions in the late time phase. The erosional/relaxational contribution can then be obtained by subtracting the calculated diffusional contribution from the overall release for each time point (Figs. 1–3). As with all empirical models the results should be viewed with caution and should be considered together with additional evidence based on direct measurements such as swelling, erosional and textural changes with time.

From Fig. 4 and Table 1 it is apparent that the various additives cause marked differences in drug release. The most rapid overall release occurs in the presence of citric acid, while adding glycine results in the slowest release. Furthermore most release profiles were linear for at least a portion of the overall release duration. However, NaCl, glycine and to a lesser extent NaHCO$_3$ differ from the other additives in that they reduce the diffusional contribution to the overall release rate of the drug as can be seen from the lower diffusion rate constants, the shorter duration of purely diffusional release and greater contribution due to matrix relaxation/erosion to the overall release (Figs. 1–3, Table 2). The same trend is also visible from a comparison of the diffusional and relaxational constants obtained from Eq. (3) (Table 3). The ratio of \( k_2/k_1 \) is clearly higher for glycine and NaCl when compared to the remaining formulations. This manifests itself in slower and less curvi-linear release in the early time phase, thus contributing to greater overall linearity of the profiles.

The ability of water soluble electrolytes to compete for water of hydration, thereby causing the dehydration of hydrophilic colloids leading to ‘salting out’, precipitation or gelling, is well documented [16,17]. The ability of electrolytes to effect such changes is generally dependent on the extent to which the anions and cations can be hydrated and can be predicted from the Hofmeister series [25]. The reduced drug diffusion in the presence of NaCl and glycine may therefore in part be due to the competition for the limited amount of water within the gel and the preferential hydration of the highly soluble, ionizable substances at the expense of the polymer. In terms of this proposed mechanism, NaCl, which is able to dissociate into two small highly polarizable ions, would be expected to be more efficient than glycine. A further consideration is that due to the limited free water and high concentration of electrolyte within the gel, drug
Fig. 1. Dissolution profiles for formulations containing glycine, NaCl and Avicel. Key: ▼, actual release; ♦, calculated diffusion; ●, calculated erosion (S.D.<10%).

Fig. 2. Dissolution profiles for formulations containing no additive (control), citric acid and sodium bicarbonate (NaHCO₃). Key: ▼, actual release; ♦, calculated diffusion; ●, calculated erosion (S.D.<10%).
Fig. 3. Dissolution profiles for formulations containing Emcompress, sucrose and lactose. Key: ▼, actual release; ◊, calculated diffusion; ●, calculated erosion (S.D. <10%).

Table 1

<table>
<thead>
<tr>
<th>Additive</th>
<th>% Released 3 h</th>
<th>t_{50%}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>27.04</td>
<td>8.00</td>
</tr>
<tr>
<td>Sucrose</td>
<td>23.76</td>
<td>9.50</td>
</tr>
<tr>
<td>Lactose anhydrous</td>
<td>23.73</td>
<td>10.50</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>22.57</td>
<td>11.00</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>21.91</td>
<td>11.00</td>
</tr>
<tr>
<td>Control (no additive)</td>
<td>23.10</td>
<td>10.00</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>17.69</td>
<td>13.00</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>16.01</td>
<td>11.00</td>
</tr>
<tr>
<td>Glycine</td>
<td>17.10</td>
<td>13.50</td>
</tr>
</tbody>
</table>

Soluble sugars such as sucrose and sorbitol are also known to compete for water of hydration with hydrophilic colloids and have been reported to depress the gel point of HPMC [16]. However, in the current formulation sucrose and lactose were no more, or slightly less effective than the control formulation in terms of controlling early diffusional solubility would be expected to be reduced. In the case of NaHCO₃, drug solubility may also be reduced due to free base formation in the alkaline microenvironment of the gel matrix. However, it should be noted that NaHCO₃ appears to be incompatible with guar, resulting in color change and very sticky granulations with poor compression properties.
release. It therefore seems that these hydrophilic additives mainly served to enhance water diffusion into the gel matrix and thus by implication diffusion of drug out of the matrix, resulting in rapid nonlinear initial release of drug. Their effect on matrix erosion/relaxation appears modest.

Similarly, the presence of dicalcium phosphate in the guar gel matrices seems to have a minimal effect in terms of diffusion control when compared to the control formulation. According to the lyotropic series Ca\(^{2+}\) salts would be expected to be more effective than Na\(^+\) salts and phosphate ions would precede Cl\(^-\) ions in terms of their extent of hydration and salting out ability. However, the limited solubility of dicalcium phosphate in the gel environment may partly explain the negligible impact of this additive.

The formulation containing microcrystalline cellulose had the most curved release profile with a distinctly slower instantaneous rate of release and a tendency for tailing off in the late time phase. It is clear that for this formulation, overall release is predominantly attributable to the contribution made by Fickian diffusion with a minimal contribution made by matrix erosion/relaxation (Fig. 1, Tables 2 and 3). Furthermore from visual observations it was evident that guar and microcrystalline cellulose combine to form a non-disintegrating, swellable matrix. Factors that may contribute to the formation of such a non-disintegrating, spongy matrix include the fact that swelling in the microcrystalline cellulose particles is limited to the amorphous domains while the denser crystalline regions do not swell and prevent dissolution [25]. The swelling particles of microcrystalline cellulose thus remain within the hydrating matrix, and do not diffuse out as would be expected from the soluble sugars and electrolytes.

Furthermore there is the likelihood of weak physical cross-linking between microcrystalline cellulose and guar.

The ability of guar to absorb onto hydrated

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### Table 2
Fitting results for purely Fickian diffusion (Eq. (4))

<table>
<thead>
<tr>
<th>Additive</th>
<th>Slope ((k))</th>
<th>Intercept</th>
<th>Duration of Fickian release (h)</th>
<th>(r^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>26.22</td>
<td>-14.73</td>
<td>7.0</td>
<td>0.9982</td>
</tr>
<tr>
<td>Sucrose</td>
<td>23.17</td>
<td>-13.26</td>
<td>4.5</td>
<td>0.9993</td>
</tr>
<tr>
<td>Lactose anhydrous</td>
<td>21.43</td>
<td>-10.54</td>
<td>6.5</td>
<td>0.9997</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20.62</td>
<td>-10.38</td>
<td>8.5</td>
<td>0.9994</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>20.23</td>
<td>-10.43</td>
<td>5.5</td>
<td>0.9997</td>
</tr>
<tr>
<td>Control (no additive)</td>
<td>19.33</td>
<td>-7.84</td>
<td>5.0</td>
<td>0.9992</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>18.58</td>
<td>-11.95</td>
<td>5.5</td>
<td>0.9983</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>16.99</td>
<td>-11.22</td>
<td>3.5</td>
<td>0.9984</td>
</tr>
<tr>
<td>Glycine</td>
<td>13.41</td>
<td>-4.41</td>
<td>4.0</td>
<td>0.9997</td>
</tr>
</tbody>
</table>

### Table 3
Fitting results for Eq. (3)

<table>
<thead>
<tr>
<th>Additive</th>
<th>Fickian rate constant (k_1) (% h(^{-0.41}))</th>
<th>Relaxational rate constant (k_2) (% h(^{-0.86}))</th>
<th>(k_2/k_1)</th>
<th>(r^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>8.364</td>
<td>5.130</td>
<td>0.613</td>
<td>0.9987</td>
</tr>
<tr>
<td>Sucrose</td>
<td>7.410</td>
<td>4.440</td>
<td>0.599</td>
<td>0.9980</td>
</tr>
<tr>
<td>Lactose anhydrous</td>
<td>8.432</td>
<td>3.718</td>
<td>0.441</td>
<td>0.9980</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>8.289</td>
<td>3.418</td>
<td>0.412</td>
<td>0.9985</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>6.764</td>
<td>3.994</td>
<td>0.590</td>
<td>0.9972</td>
</tr>
<tr>
<td>Control (no additive)</td>
<td>7.358</td>
<td>4.149</td>
<td>0.564</td>
<td>0.9943</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>4.305</td>
<td>4.102</td>
<td>0.953</td>
<td>0.9992</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.132</td>
<td>6.141</td>
<td>46.59</td>
<td>0.9967</td>
</tr>
<tr>
<td>Glycine</td>
<td>2.302</td>
<td>4.608</td>
<td>2.002</td>
<td>0.9915</td>
</tr>
</tbody>
</table>
cellulose surfaces via hydrogen bonding is well documented and has long been exploited in the paper industry [26]. As indicated earlier, guar is thought to be an especially efficient additive as both the d-galactopyranosyl and d-mannopyranosyl units of guar have cis-hydroxyl groups, which confer strong hydrogen bonding ability on the polymer. In such a system one would therefore expect to find reduced polymer matrix dissolution and restrained swelling and water uptake.

As with microcrystalline cellulose, drug release from the formulation containing citric acid is predominantly diffusion mediated. However, unlike microcrystalline cellulose, citric acid appears to promote very rapid drug diffusion ($k = 26.22\% h^{-0.43}$). This would imply very rapid water ingress, swelling and polymer hydration. While citrate$^{3-}$ ions are extremely well hydrated and would be expected to compete effectively for water, thus reducing the extent of polymer hydration, it is clear that in the acidic dissolution medium, the undissociated citrate molecules are ineffective in this regard and in fact appear to be increasing drug and polymer solubility. In the case of citric acid and guar a further consideration may be that the rapid ingress of water is also related to the tendency of the anhydrous citric acid formed during granule drying to rapidly hydrate thus contributing to very large stress relaxation within the matrix which greatly enhances the swelling of the system.

3.2. Water uptake and mass loss studies

In an effort to obtain further evidence for the postulated differences in release mechanism attributed to the various additives, additional water uptake, matrix mass loss and textural analysis studies were conducted. It was found that water uptake and mass loss kinetics were generally well correlated with drug release kinetics (Fig. 5). Furthermore, consistent with the ability of the soluble electrolytes (NaCl and glycine) to reduce the initial diffusional contribution to overall drug release, these substances show lower initial water uptake when compared to the control formulation and soluble sugars (Fig. 6). This observation would therefore tend to confirm that the presence of highly soluble, ionizable water competitive substances in the matrix results in their preferential hydration, reducing the initial rate and extent of hydration of the polymer and drug. Conversely, the more rapid initial diffusional release in the presence of soluble sugars (lactose, sucrose) is correlated with significantly greater water uptake in the same time period, indicating that those materials tend to promote guar hydration and swelling in the tablet matrix. This may be related to their osmotic effect.
Alternatively the rapidly leaching soluble sugars may also act as channel forming agents, resulting in increased matrix porosity. In contrast, addition of microcrystalline cellulose resulted in significantly lower water uptake. As noted earlier, reduced volume expansion and inhibited swelling and therefore limited polymer relaxation are usually expected in cross-linked polymer systems. Interestingly, dicalcium phosphate (Emcompress) also showed lower dissolution medium uptake.

Further evidence of a non-disintegrating cross-linked guar-microcrystalline cellulose gel system is also obtained from the matrix mass loss studies (Fig. 7), which showed that most of the mass loss (~30%) could be accounted for in terms of the mass of released drug, thus indicating minimal polymer erosion. In contrast, in accordance with their large calculated erosional/relaxational contribution to overall drug release, the mass loss kinetics for the glycine and NaCl formulations are relatively linear with ~80% mass loss over 24 h indicating extensive matrix erosion. For the lactose, dicalcium phosphate and control formulations, matrix erosion is somewhat lower (~70% in 24 h).

### 3.3. Textural analysis

While water uptake studies provide a macroscopic picture of overall swelling, they do not provide detailed information on the nature of the gel and the state of water. $^1$H-NMR imaging studies have demonstrated the existence of polymer concentration and water mobility gradients (rather than discrete regions

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**Fig. 6.** Medium uptake at 6 h for formulations containing different additives. *Significantly different from control ($P<0.05$, Tukey’s).

**Fig. 7.** Mass loss kinetics for formulations containing various additives (18%). Based on three tablets removed at each time point from the dissolution apparatus. Conditions as for dissolution testing.
delineated by sharp fronts) within the hydrating polymer matrix [5]. The polymer/water concentration gradients also result in textural and physico-mechanical changes in the gel layer of matrix tablets which can be accurately detected by textural analysis and can be correlated with results obtained from $^1$H-NMR [27].

A typical force–distance profile is given in Fig. 8. This allowed the detection of various phases within the gel region that could also be correlated with microscopy. The phases were distinctly different, yet could not be delineated by sharp boundaries. In the case of the glycine formulation an outer fully hydrated gel layer could be correlated with the region of negligible penetration force. Adjoining this a smooth, swollen, opaque region was observed. This region most likely consists of partially swollen, infiltrated polymer, with a substantial amount of drug in the undissolved state due to the limited water activity. This region corresponds to a steadily increasing penetration force and smoothly transitions into a more rigid moist region which shows signs of water penetration, but as yet negligible swelling. The slope then increases toward infinity as the glassy core is penetrated.

Fig. 9 shows that the growth of the fully hydrated gel layer (region A in Fig. 8) continues throughout the swelling period for all the formulations, therefore no constant gel layer thickness is attained. The growth in gel layer thickness can be approximately correlated with the observed pattern for medium uptake (Fig. 5). The most rapid increase in fully hydrated gel layer thickness was observed for citric acid, followed by an intermediate group consisting of NaHCO$_3$, sucrose and lactose. The remaining additives result in slower increases in fully hydrated gel layer thickness. Consistent with the water uptake studies microcrystalline cellulose (Avicel) swells the slowest, and NaCl shows slower growth in gel layer thickness than glycine.

The effect of the various excipients on gel strength was investigated by calculating the work of penetration from the various force–displacement profiles. As can be seen in Fig. 10, in the presence of NaCl and glycine, gel strength increases rapidly between 0 and 3 h as compared to the control formulation. However, after 6 h the gel strength decreases significantly for these formulations. The NaHCO$_3$
crocrystalline cellulose–guar matrix, this formulation shows steadily increasing gel strength which also correlates with its minimal erodibility. It therefore appears as postulated earlier, that the highly soluble electrolytes (glycine and NaCl) retard the hydration of the polymer and dissolution of the drug during the early time phase. This results in markedly harder peripheral gel matrices and reduced drug diffusion during the early time phase. However, water penetration as such is not inhibited. Furthermore due to their high solubility and tendency to be preferentially hydrated, glycine and NaCl diffuse out of the matrix rapidly, resulting in progressively weaker gels which are then more susceptible to erosion. To a lesser extent this behavior is also shown by NaHCO₃. Appropriately chosen excipients therefore have the potential to influence the nature of guar gel matrices in a time-dependent manner, thus compensating for the increased gel thickness and diffusional path length due to ongoing swelling. However additional factors need to be considered as glycine, which generally is expected to be less effective in inhibiting hydration than NaCl, nevertheless achieves a slower release. In contrast to the above named behavior the remaining formulations tend to hydrate more rapidly during the early time phase thus promoting more rapid diffusional release. These formulations then maintain or increase their gel strength with time which is also reflected in their lower erodibility. It should also be noted that the systems described here are complex and non-heterogeneous in nature which would also be expected to have an impact on swelling and drug release.

4. Conclusion

It has been shown that in guar-based matrix systems the physico-chemical nature of the added excipients influences swelling, matrix erosion and verapamil release kinetics and mechanism. The appropriate choice of intragranular additive can therefore be used as a tool for release modulation. In part the effect of various excipients can be explained in terms of their effect on the structure of free water within the hydrating gel matrix and their simultaneous interaction with the polymer. This results in
structural and textural differences in the hydrating matrices, which vary with time. In particular, certain ionic and highly soluble excipients such as glycine and NaCl are able to reduce initial rapid drug release through what appears to be initial competition for the limited water within the gel, thus leading to slower polymer relaxation controlled hydration. In addition, the observed interaction between microcrystalline cellulose and guar, while not ideal in the context of the current study, may be useful for other controlled release applications and deserves further investigation.

References