Alginate-diltiazem hydrochloride beads: optimization of formulation factors, \textit{in vitro} and \textit{in vivo} availability

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Alginate beads containing diltiazem hydrochloride (DTZ) were prepared by the ionotropic gelation method. The effects of various factors (alginate concentration, additives type, calcium chloride concentration and curing time) on the efficiency of drug loading were investigated. The formulation containing a mixture of 0.8% methylcellulose (MC) and 4% alginate cured in 2% calcium chloride for 6 h was chosen as the best formula regarding the loading efficiency. The release rate of DTZ from various beads formulations was investigated. The release of drug from alginate beads followed two mechanisms; by diffusion and relaxation of the polymer at pH 1.2, whilst diffusion and erosion are at pH 6.8. The \textit{in vitro} release of DTZ from MC-alginate beads showed an extended release pattern which was compared with that from commercially available sustained-release (Dilzem\textsuperscript{®} SR) and fast release tablets (Dilzem\textsuperscript{®}). Thermal analysis revealed that the drug was molecularly dispersed in the beads matrix. Although the release characteristics of DTZ from Dilzem\textsuperscript{®} SR and MC-alginate beads were completely different, the bioavailability of DTZ in dogs was comparable as measured by AUC, MRT and relative bioavailability. The absolute bioavailability of MC-alginate beads and Dilzem\textsuperscript{®} SR was 88 and 93%, respectively.

Keywords: Alginate beads, diltiazem hydrochloride, formulation factors, \textit{in vitro} and \textit{in vivo} availability, microencapsulation.

Introduction

Alginites (polysaccharides) are obtained from marine brown algae, known to be haemocompatible, and do not accumulate in any organ of the human body. Alginites can be considered as block polymers which mainly consist of mannuronic acid (M), guluronic acid (G) and mannuronic-guluronic (MG) blocks. The gelation of alginate is caused by forming an egg-box junction to associate divalent metal ions with the GG block of alginate polymer chain (Mirghani \textit{et al.} 2000). Sodium alginate has been used as a matrix material in medicine to achieve a controlled release drug delivery due to its hydrogel forming properties (Badwan \textit{et al.} 1985, Pepperman \textit{et al.} 1991, Pillay \textit{et al.} 1998).

The active substance of this investigation, diltiazem HCl (DTZ), is a calcium antagonist benzothiazepine derivative used for treatment of angina and hypertension. It has a short half life of 3–6 h, its water solubility exceeds 50% and the oral absorption is greater than 90%. The bioavailability of DTZ ranges from 30–

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60% due to extensive variable first pass metabolism (AHFS 1997). Based upon these properties, there is a great need for the introduction of a new controlled release formulation of DTZ.

The main objective of the present study is to formulate DTZ in alginate beads to control the drug release. The effect of some formulation parameters on drug entrapment efficiency, namely concentration of alginate as well as of calcium chloride, the contact time with hardening agent and the addition of pectin or methylcellulose to alginate were investigated. The effect of different additives on the in vitro release behaviour of DTZ from alginate beads was examined. Furthermore, the in vivo sustained release characteristics of alginate gel beads were evaluated in beagle dogs and compared with those of intravenous injection and commercial sustained release DTZ preparation (Dilzem SR).

Materials and methods

Materials

Diltiazem hydrochloride was obtained as a kind gift from Riyadh Pharma (Riyadh, Saudi Arabia). Alginate (Alg), pectin 250 grade (pect.), methycellulose (MC) and acetonitrile (HPLC grade) were obtained from BDH Chemicals Ltd (Poole, England). Calcium chloride was provided from Fluka Chemie AG (Switzerland). All other chemicals and solvents were of analytical grade.

Methods

Formulation of DTZ-calcium alginate gel beads. Solutions of sodium alginate (1–4%), pectin (4%), alginate-pectin 4% (1:1) or alginate–methylcellulose (4%:0.8%) were prepared by the addition of the polymers to 0.03 M sodium hydroxide. Each solution was magnetically stirred gently at 25°C for 15 min. When complete solubility of the polymer was attained, the drug was added in a ratio of 2:1 (polymer:drug) and homogeneously dispersed. The drug–polymer dispersions were sonicated for 10 min in an ultrasonic bath to remove air bubbles that might be formed during the stirring process. The dispersions were added via an 18-gauge needle into a gently agitated solution of calcium chloride. The concentration of calcium chloride solution was 2% w/v, unless otherwise stated. For each dispersion, the droplets instantaneously gelled into discrete DTZ-calcium alginate gel discs upon contact with the surface of the calcium chloride solution. Each batch of DTZ-alginate gel beads was left in the dark for 6 h to cure in the calcium chloride solutions unless otherwise stated. The calcium chloride solutions were decanted and each batch was washed three times with 500 ml deionized distilled water. The batches were separately spread on a stainless steel tray or aluminium foil and vacuum-dried at 25°C for 24 h. The dried batches were stored in airtight glass vials. Different calcium chloride concentrations (0.1–4%) and curing time (0–24 h) were utilized to optimize the drug loading efficiency.

Determination of DTZ content in the calcium alginate gel beads. The drug loading efficiency of calcium alginate gel beads was determined using the following equation:

\[
\text{Drug loading efficiency (\%)} = \left( \frac{AQ}{TQ} \right) \times 100
\]
where, AQ and TQ are the actual and theoretical quantity of drug present in the calcium alginate beads, respectively.

Twenty milligram of DTZ beads from each batch were initially stirred in 3 ml sodium citrate solution (1% w/v) until complete dissolution. One millilitre of methanol was added to sodium citrate solution to gel the solubilized calcium alginate and further solubilize DTZ. This solution was vacuum filtered through a 0.45 μm Millipore membrane filter. The filtrate was subjected to UV spectroscopy to determine the drug content at $\lambda_{\text{max}}$ 240 nm after suitable dilution. No interference due to the dissolved alginate, pectinate or methylcellulose was evident.

**In vitro dissolution testing.** Dissolution studies were performed in triplicate using the USP 23 dissolution apparatus II (paddle method) at 50 rpm. The media used were either 900 ml deaerated 0.1 N (pH 1.2) HCl or phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C. Samples were taken at appropriate time intervals and assayed spectrophotometrically at $\lambda_{\text{max}}$ 240 nm.

Dissolution rate testing was performed for drug powder (90 mg), beads containing equivalent amount of 90 mg drug and commercial preparations; fast and sustained release.

**Swelling studies.** Swelling properties of the beads were studied by soaking the beads at 37 ± 1°C in 0.1N HCl or phosphate buffer pH 6.8 in a glass beaker. The beads were removed at different time intervals and weighed after drying the surface water. The ratio of water uptake was calculated as:

\[
\text{Ratio of water uptake} = \frac{(\text{wet weight} - \text{dry weight})}{(\text{dry weight})}
\]

All mass measurements of the swollen beads were taken on single pan balance (Mettler AE 240S, Switzerland), having an accuracy up to fifth decimal.

**Determination of calcium content in the beads.** Alginate beads (20 mg) were dissolved in 10 ml concentrated nitric acid at 50°C. The samples were diluted with lanthanum oxide 10 000 ppm (releasing agent). Calcium content was determined by atomic absorption spectroscopy (AA-6701F Atomic absorption flame emission spectrophotometer, Shimadzu, Japan).

**Differential scanning calorimetry (DSC).** The DSC thermograms were recorded on a general V1.0J Dupont 9900 thermal analyser (Dupont, Wilmington, DE, USA) calibrated with indium (99.99%). The DSC studies on the samples were performed by heating samples at a heating rate of 5°C/min over a temperature range of 25–325°C in closed aluminium pans under an argon purge.

**In vivo study design.** Five beagle dogs (16.1 ± 1.48 kg) were used in the present study. DTZ was administered on three occasions separated by at least 1 week between each treatment. The dogs were starved overnight and 2 h post administration.

DTZ pure powder was administered (20 mg) intravenously as an isotonic saline solution (5 mg/ml) in the first treatment period. In the second period, DTZ was administered orally as sustained release commercial tablets (90 mg) by gastric intubation. The beads prepared in the laboratory were filled in hard gelatin
capsules (equivalent to 90 mg DTZ) and administered orally in the third period of treatment.

Multiple blood samples (5 ml) were collected in heparinized vacutainer tubes before and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 h post-intravenous administration and before and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h post-oral administration. The plasma was then separated after centrifugation and stored frozen at −20°C pending analysis.

**Analysis of plasma samples.** DTZ plasma concentration was measured using a sensitive high performance liquid chromatography assay. The HPLC system (Jasco, UV-1575 detector, Jasco, PU-1580 pump, Jasco Corporation, Tokyo, Japan, Shimadzu C-R 6A Chromatopac integrator, Tokyo, Japan) was used in the reversed-phase mode. Analysis was performed on a Novapack C18 packed column (300 mm length × 4.6 mm id.). The mobile phase consisted of 65% phosphate buffer pH 3.5 and 35% acetonitrile. The final pH was then adjusted to pH 3.5 using orthophosphoric acid. Amytriptyline was used as an internal standard. The UV detector was adjusted to 240 nm. Calibration curve was constructed using blank plasma spiked with drug (10–500 ng/ml) and 10 µl of internal standard (100 µg/ml).

**Pharmacokinetic analysis.** Pharmacokinetic parameters for DTZ following DTZ administration were determined from plasma concentration–time data. The maximum plasma concentration ($C_{\text{max}}$) and the corresponding time ($T_{\text{max}}$) were obtained from the individual plasma concentration-time curve of each dog. The area under the curve (AUC) and the area under the first moment curve (AUMC) were estimated using a linear trapezoidal rule with the aid of the Stripe programme. The mean residence time of the drug in the body (MRT) and the absolute bioavailability (F) of the prepared beads and the commercial sustained release tablets were calculated using the following equations (Gibaldi 1991):

\[
\text{MRT} = \frac{\text{AUMC}}{\text{AUC}_{\infty}},
\]

\[
F = \left( \frac{\text{AUC}_{\text{po}}}{\text{AUC}_{\text{iv}}} \right) \times \left( \frac{\text{dose}_{\text{iv}}}{\text{dose}_{\text{po}}} \right)
\]

where AUMC is the area under the first momentum curve, AUC$_{\text{po}}$ and AUC$_{\text{iv}}$ are the area under the curve after oral and intravenous administration, respectively.

**Statistical analysis.** Statistical evaluations of data were performed using analysis of variance (ANOVA) with the aid of a mixed model least-squares and maximum likelihood computer program PC-2.

**Results and discussion**

**Optimization of drug loading**

The formulation of the calcium alginate beads is based on both the concentration of sodium alginate and the ability of calcium ions to cross link with sodium alginate. The degree of cross linking is dependent on both the concentration of the calcium chloride solution and the time of contact of the beads with this solution. To optimize the parameters affecting the formulation of beads, various factors were evaluated; sodium alginate concentration, calcium chloride concentration,
curing time and incorporation of methylcellulose and pectin into alginate as a matrix for beads.

Three different concentrations of sodium alginate were examined namely: 2, 3 and 4% (calcium chloride 2% as a cross linking agent for 6h). Higher loading efficiency was obtained as the concentration of alginate increased (figure 1(a)). This may be attributed to the greater availability of active calcium-binding sites in the polymeric chains and, consequently, the greater degree of cross linking as the quantity of sodium alginate increased. Yotsuyanagi et al. (1987) demonstrated that the diffusion coefficient of benzoic acid, indigo carmine, bromocresol green and rose bengal became smaller as the sodium alginate concentration increased. Therefore, they argued that, in view of this phenomenon, higher drug loading capacities might be obtained with increasing sodium alginate concentration.

Figure 1. Effect of (a) sodium alginate concentration, (b) calcium chloride concentration, (c) curing time, and (d) additives on drug loading efficiency of alginate beads.
Increasing calcium chloride concentration from 0.1 to 2% elevated DTZ loading from 19 to 54% (figure 1(b)) for beads prepared using 4% alginate and 6 h curing time. This may be explained by the increase in the gel strength as the calcium ions increased. From the results of calcium ion determination (figure 2), it is obvious that increasing calcium chloride concentration produced beads with higher levels of calcium ions. Consequently, the cross linking of the polymer and compactness of the formed insoluble matrices also increased. This would result in more drug entrapment in the beads. These results are in agreement with Takka et al. (1998) and Mirghani et al. (2000). On the other hand, Ostberg et al. (1994) reported that less drug encapsulated at higher calcium concentration. It was also found that further increase in the concentration of calcium chloride (up to 4%) did not enhance the drug loading (figure 1(b)). This could be due to possible saturation of calcium binding sites in the guluronic acid chain, preventing further calcium ion entrapment and, hence, cross linking was not altered with higher concentrations of calcium chloride solution.

Yotsuyanagi et al. (1987) reported that apparent gelation of the calcium alginate matrices seemed to occur rapidly, however, they observed that further rearrangement of the gel structure continued for a long period. Therefore, in order to optimize the cross linking of the alginate matrix and, consequently, the drug loading, different calcium chloride exposure times (curing time) were evaluated to establish the optimum time to attain maximum cross linking and loading efficiency.

The immediate separation of beads (prepared using 4% sodium alginate and cross linked with 2% calcium chloride) from calcium chloride solution resulted in the highest drug content (75%) compared to 68, 63 and 54% after 2, 3 and 6 h of contact. The contact time with calcium chloride for 12 and 24 h did not further
improve the loading efficiency (figure 1(c)). The initial 25% loss of drug loaded could be due to high water solubility and rapid diffusion of DTZ through the weakly cross linked alginate beads. The entrapment efficiency decreased with an increase in curing time (0–6 h) due to the increased release of DTZ from the matrix at longer exposures. However, constant drug loading was achieved at 6 h, with no further decrease after 12 and 24 h of curing. This could be due to the formation of tight junction zones between the calcium ions and the active sites on the guluronic acid chain. The tight junctions may have produced high strength and an inflexible polymeric chain. Consequently, the drug was entrapped in a highly bound calcium alginate matrix from which no further drug release occurred.

In an attempt to modify the drug encapsulation efficiency, a copolymer in the form of cellulose derivative (MC) and pectin was added to sodium alginate. Methylcellulose is a cellulose ether in which the methyl group has been substituted for the hydroxyl group on the 2-glucopyranose residues. Low methoxy pectin has the ability to form gels with divalent cations and has been used in the production of calcium pectinate, intended for controlled release drug delivery (Pillay and Fassihi 1999a). The rank order for the loading efficiency of the prepared beads was Alg<pect<Alg-pect<Alg-MC (figure 1(d)). The highest efficiency of drug loading was obtained for beads containing MC. This polymer (MC) has been reported to increase the degree of agglomeration of alginate beads (Chan et al. 1997). It has also been reported (Swarbrick and Boylan 1992) that the gelling temperature of MC can be lowered by adding sugar or carbohydrate molecules. This may result in the formation of a more rigid gel structure around the particles leading to high drug encapsulation efficacy. Chan et al. (1997) also reported that less hydrophilic cellulose derivatives such as MC found to increase the encapsulation efficiency of sulphaguanidine in alginate beads. The maximum drug loading efficiency (67%) obtained after addition of MC is reasonable compared to the reported low encapsulation efficiency for low molecular weight drugs in alginate beads. Hari et al. (1996) reported 4% loading for nitrofurantoin, while 32% loading for indomethacin was achieved by Shiraishi et al. (1993). The porosity of alginate beads (Liu et al. 1997, Türkoglu et al. 1997) could be responsible for the low encapsulation efficiencies. Moreover, the encapsulation efficiencies of water soluble drugs are in general lower than that for slightly soluble or insoluble drugs (Aslani and Kennedy 1996).

The formula containing a mixture of methylcellulose and alginate was chosen for further swelling and in vivo studies as it is considered to be the best formula from the loading efficiency point of view.

Swelling study

The swelling properties of Alg-MC beads were studied by measuring the water uptake at certain time intervals in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8). Being polyelectrolyte, alginate can exhibit swelling properties that are sensitive to the pH. The results of water uptake by the beads are displayed in figure 3. In 0.1 N HCl, the ratio of water uptake was low and independent of time relative to that obtained at pH 6.8. Maximum water uptake was obtained at 2 h in phosphate buffer (pH 6.8), after which erosion and breakdown of beads occurred. These results suggest that the dried gel particles will swell slightly in the stomach and, as they are subsequently transferred to upper
intestine, the particles will begin to swell more and behave as matrices for controlled release of incorporated drug. However, they are subject to erosion in the lower intestine.

**Thermal studies**

The DSC thermograms of pure drug, sodium alginate, pectin, methyl cellulose, pectin beads, alginate beads, alginate-methylcellulose and alginate–pectin beads are shown in figure 4. Diltiazem HCl exhibited a sharp endothermic peak at 215°C. The peak of the drug did not appear in the thermogram of any type of the prepared beads containing the drug. This may indicate that most of the drug was uniformly dispersed at the molecular level in the beads.

**Release studies**

The release of DTZ from the prepared beads was performed in 0.1 N HCl for only 2 h (approximately the residence time in the stomach) and in phosphate buffer pH 6.8 for 7 h (to simulate the intestinal conditions). Figures 5(a) and (b) showed fast release of drug from alginate beads containing DTZ, since 48 and 89% of drug released within 1 h in 0.1 N HCl and at pH 6.8, respectively.

It was observed from the swelling study that alginate beads had swollen in phosphate buffer pH 6.8 more than in 0.1 N HCl. The release will depend on diffusion of DTZ through the insoluble matrix of alginate polymer in 0.1 N HCl. On the other hand, rapid swelling and erosion of beads prepared from alginate were observed at pH 6.8. Erosion could occur through degradation of alginate backbone into smaller molecular weight components. In addition, the ion ex-
Figure 4. DSC thermograms of pure drug, sodium alginate, pectin, methylcellulose, pectin beads, alginate beads, alginate-methylcellulose and alginate-pectin beads.
change with phosphate buffer causes the erosion of the beads, which greatly increases the drug release rate (Türkoglu et al. 1997). The release of DTZ from pectin beads in 0.1 N HCl was not significantly different from that of alginate beads while it showed faster release in buffer pH 6.8 due to the brittle nature of

Figure 5. The *in vitro* release profile of DTZ from various formulations in (a) 0.1 N HCl, and (b) phosphate buffer, pH 6.8.
pectin beads and faster solubility of pectin at this pH than alginate as reported by Pillay and Fassihi (1999b).

In an attempt to retard or sustain DTZ release, pectin and methylcellulose were added to the alginate matrix. The rank order for the rate of drug release from the beads in 0.1 N HCl was as follows: Alg-MC > Alg-pect->pect>Alg. Addition of pectin to alginate in a ratio of 1:1 enhances the rate of drug release to some extent. Incorporation of low methoxylated pectin together with alginate appears to influence the degree of cross-linking and results in enhancement of drug release in 0.1 N HCl (Pillay and Fassihi 1999b). Addition of MC to alginate resulted in highest drug release rate in 0.1 N HCl. This could be due to protonation of ether linkage of MC in acidic medium and, consequently, the tortuosity of hydrated MC molecules decreased leading to a more rapid drug release (Lapidus and Lordi 1966).

At pH 6.8, the rank order of drug release was pect> Alg> Alg-pect> Alg-MC. As expected, the lowest drug release rate at this pH was obtained from beads prepared with MC of high viscosity grade. Its existence with alginate resulted in decreased hydration and gelling temperature of MC (Swarbrick and Boylan 1992). This could lead to formation of a more viscous, less hydrated gel layer around DTZ molecules that resulted in decreasing the rate of drug release. DTZ release from any type of prepared beads was significantly suppressed compared to the dissolution profile of drug powder in 0.1 N HCl or buffer pH 6.8 (figures 5(a) and (b)).

Figure 6 shows the release of DTZ from the prepared Alg-MC beads, the commercial, both fast and sustained release tablets. The release of DTZ from the prepared beads in buffer pH 6.8 was slower than that obtained from commercial fast release tablets. However, it was faster than the commercial sustained release
product. It has been reported earlier that the polysaccharide beads have rapid \textit{in vitro} release, and their \textit{in vivo} profile did not reflect the \textit{in vitro} release profile (Imai \textit{et al.} 2000).

In general, the release mechanism from a swellable hydrophilic system containing different ratios of polymeric materials and a highly soluble drug will be influenced by a number of parameters (Kim and Fassihi 1997). These include the rate of fluid infusion into the matrix, the rate of matrix swelling, and molecular diffusion of the drug through the swollen gel layer, polymer relaxation and chain disentanglement, nonhomogenous gel microstructure and dissolution/erosion and total disentanglement at the dissolution front.

To investigate the release mechanism, the initial portion of the release curve ($M_t / M_\infty < 0.6$) was analysed using the following equation (Peppas 1985, Ritger and Peppas 1987):

$$M_t / M_\infty = kt^n$$

where $n$ represents the diffusional exponent and $k$ is a parameter characteristic of the polymer network and active agent. The results are shown in table 1. Values of the exponent $n$ lying between 0.5–1 for all formulations indicate a non-Fickian transport controlled by diffusion and relaxation of the polymer. The dried alginate beads swelled slightly in 0.1 N HCl. However, they swelled more at pH 6.8 and underwent erosion. So the release of drug from beads took place by both diffusion through the swollen matrix and relaxation of the polymer in 0.1 N HCl. However, at pH 6.8, the release was due to both diffusion and erosion mechanisms. These results are in accordance with those obtained by Takka \textit{et al.} (1998).

\textbf{In vivo study}

The mean plasma concentration as a function of time after oral administration of 90 mg single dose of diltiazem HCl sustained release commercial tablets and, as prepared alginate-methylcellulose beads, is shown in figure 7. The pharmacokinetic parameters for both formulations are illustrated in table 2. The absorption from sustained release commercial tablets was faster, reaching peak plasma concentration in 2.6 ± 0.9 h, whereas, following administration of Alg-MC beads, the mean $T_{\text{max}}$ was 4.4 ± 1.6 h post-dosing. The peak plasma concentration ($C_{\text{max}}$) was lower following the administration of Alg-MC beads (308.3 ± 181 ng/ml) compared to the commercial sustained release tablets (456.5 ± 166 ng/ml). Statistical difference was found between the two treatments in both the time and the magnitude of the peak ($p < 0.05$). However, no statistical difference was

<table>
<thead>
<tr>
<th>Type of beads</th>
<th>$n$</th>
<th>$k$</th>
<th>$r$</th>
<th>$n$</th>
<th>$k$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate</td>
<td>1.00</td>
<td>-0.16</td>
<td>0.975</td>
<td>0.57</td>
<td>0.927</td>
<td>0.998</td>
</tr>
<tr>
<td>Pectin</td>
<td>0.91</td>
<td>0.06</td>
<td>0.979</td>
<td>0.66</td>
<td>0.933</td>
<td>1.000</td>
</tr>
<tr>
<td>Alginate-pectin</td>
<td>0.95</td>
<td>0.07</td>
<td>0.997</td>
<td>0.88</td>
<td>0.287</td>
<td>0.994</td>
</tr>
<tr>
<td>Alginate-MC</td>
<td>0.79</td>
<td>0.36</td>
<td>0.985</td>
<td>0.53</td>
<td>0.788</td>
<td>0.990</td>
</tr>
</tbody>
</table>

Table 1. Kinetic constants ($k$), diffusional exponents ($n$) and correlation coefficients ($r$) by linear regression of ln($M_t / M_\infty$) vs ln$t$. 

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detected between the two treatments with respect to the area under the plasma concentration-time curve (AUC\textsubscript{0–\textalpha}), indicating a comparable extent of absorption. In addition to the effect of the Alg-MC matrix, the delayed absorption of DTZ from alginate beads could also be due to the possible floating ability of alginate beads on the surface of the fluid of the stomach (as observed during invitro release studies). This is an interesting property of the beads, as a sustained-release oral delivery system has been achieved by using formulations that float on gastric juice (El-Kamel \textit{et al.} 2001).

A good parameter for evaluation of the sustained release formulations is the absorption rate, which can be calculated by division of \(C\text{\textsubscript{max}}\) by AUC (Gibaldi 1991). The rate of absorption of DTZ from alginate-MC beads (0.11 h\textsuperscript{-1}) was slightly slower than that obtained from sustained release commercial tablet (0.12 h\textsuperscript{-1}).

Table 2. The pharmacokinetic parameters of DTZ (90 mg) after oral administration of alginate-MC beads and commercial sustained releases tablet to five beagle dogs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alg-MC beads</th>
<th>Dilzem\textsuperscript{\textregt} SR tablets</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{0–24} (ng h ml\textsuperscript{-1})</td>
<td>3201.2 ± 1787</td>
<td>3477.6 ± 1336</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AUC\textsubscript{0–\textalpha} (ng h ml\textsuperscript{-1})</td>
<td>3537.1 ± 1808</td>
<td>3754.8 ± 1380</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AUMC\textsubscript{0–\infty} (ng h\textsuperscript{2} ml\textsuperscript{-1})</td>
<td>37 748.5 ± 14 254</td>
<td>36 302.3 ± 11 939</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>11.3 ± 2</td>
<td>9.88 ± 1.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>(C\text{\textsubscript{max}}) (ng ml\textsuperscript{-1})</td>
<td>308.3 ± 181</td>
<td>456.5 ± 166</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(T\text{\textsubscript{max}}) (h)</td>
<td>4.4 ± 1.6</td>
<td>2.6 ± 0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>88%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Relative bioavailability</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7. Mean plasma concentration profile after oral administration of 90 mg single dose of diltiazem HCl either as sustained release commercial tablets (Dilzem\textsuperscript{\textregt} SR) or Alg-MC beads to five beagle dogs.
The sustained release characteristics of the beads were also reflected by the mean residence time (MRT). Alginate–MC beads had a slightly higher value of MRT ($11.3 \pm 2\ h$) compared to the commercial sustained release preparation ($9.88 \pm 1.8\ h$). However no statistical significant difference ($p < 0.05$) was found between both formulations regarding MRT. Although the in vitro release characteristics were quite different between Alg-MC beads and the commercial sustained release formulation, both formulations showed approximately similar absorption profile after oral administration to beagle dogs.

The absolute bioavailability of DTZ from alginate-MC beads and commercial sustained release tablets was 88 and 93%, respectively.

Finally, it could be concluded that the proper selection of formulation conditions are very important to achieve high encapsulation efficiency and to control the release of DTZ from alginate beads. Although the release characteristics of DTZ from Dilzem® SR and alginate-MC beads were completely different in vitro, the two formulations showed bioequivalency, which suggests the successful alginate-MC beads as a sustained release formulation for DTZ.

References


