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Effect of drug solubility on release behavior of calcium polysaccharide gel coated pellets.

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ABSTRACT

The aim of this study was to investigate the effect of drug solubility on the release behavior from calcium polysaccharide gel (CaPG) coated pellets. Three different drugs with similar chemical structure, but different water solubility, namely caffeine (CAF), theophylline (TPL) and theobromine (TBR), were used. Drug-loaded spherical pellets were manufactured by an extrusion-spherization method. The CaPG was applied on the pellets loaded with different drugs by interfacial complexation coating. The encapsulation efficiency of coated pellets was found to vary from 57.6 to 84.3%, depending on the solubility of the active drug and polysaccharide type. Drug release from different uncoated pellets was relatively unaffected by pH and release media but depended mainly on drug solubility. Release behavior was significantly modified in the pellets coated with CaPG, for all of the drugs tested. Drug release from coated pellets of the different drugs showed different release kinetics. The difference in the drug release is probably due to the difference in the drug dissolution within the core, before its partition and diffusion through the CaPG coat. The CAF dissolved faster and achieved a higher concentration in solution, which drove diffusion. The release of TBR from the coated pellets was much slower than that of the CAF or TPL because of its low solubility. However, the release of all drugs was about 4 to 6-fold slower for coated than uncoated pellets, suggesting that the coating influenced the retardation of drug release from the coated pellets. Therefore, the CaPG coating may provide a sustained release delivery system for all drugs tested.
1. INTRODUCTION

Polysaccharides (i.e. alginate and pectin) are non-toxic biopolymers that are finding increasing applications in the pharmaceutical and biotechnology industries (e.g Coviello et al., 2007). Alginate and pectin are extracted from brown seaweeds and plant cell walls, respectively. Alginate is a linear chain containing (1-4)-β-D-mannuronic acid (M) and its C5 epimer (1-4)-α-L-guluronic acid (G), arranged as homopolymeric blocks (poly-M and poly-G) and as mixed blocks (MG) (Smidsrød and Draget, 1996). The poly-G blocks assume a rigid buckled ribbon conformation in solution, and it is generally thought that calcium ions can reside in a cavity between two adjacent guluronates in the poly-G block (a 2/1 helical conformation) and form a cross-link with the poly-G block of another alginate molecule (Grant et al., 1973). However, there has been some debate recently whether a 3/1 helical conformation may exist in slowly gelled systems (Li et al., 2007; Sikorski et al., 2007). It has also been shown that the MG blocks are able to interact with Ca$^{2+}$ ions (Donati et al., 2005). Pectin is a partial methyl ester of (1-4)-α-D-galacturonic acid (poly-Gal) interrupted with (1-2)-α-L-rhamnose units and other neutral sugars. Poly-Gal is almost a mirror image of poly-G; the difference is the OH configuration at C3. Low methoxy pectin, with a degree of esterification less than 50%, also forms gels with divalent ions, e.g. calcium ions (Rolin, 1993; Donati et al., 2006).

These polysaccharides, which can react with calcium ions to form cross-linked, water-insoluble gels, have been applied as potential gel coats by an interfacial complexation technique. This coating technique provides defect-free, uniform coating on solid units (Bhagat et al., 1990). Previously, spherical pellets that contain active drug, microcrystalline cellulose and calcium acetate, were prepared using an extrusion-spheronization method and then coated with various polysaccharides. Many aspects, including manufacturing, physical characteristics and performance of the coated pellets, have been examined in detail (Sriamornsak et al., 1997; 2006).
and Srimornsk and Kennedy, 2006; 2007a). Those studies were conducted to explore the physico-chemical properties and the applicability of calcium polysaccharide gel (CaPG) as a film coating intended for controlled delivery of a model drug (i.e. theophylline).

In the current study, the effect of drug solubility on pellet characteristics and release behavior from CaPG coated pellets was investigated to demonstrate whether the CaPG coating could be used to control delivery of other drugs. As shown in Fig. 1, the structurally similar drugs caffeine, theophylline and theobromine, that have different water solubilities, were employed. In recent years, some or all of these drugs (and others) have been used in several studies that investigated the effect of drug solubility on release from matrix tablets (e.g. Narisawa et al., 1995; Tahara et al., 1996; Neau et al., 1999; Efentakis et al., 2007). The general conclusion reached is that overall release is enhanced as drug solubility is increased. Neau et al. (1999) showed that drug release was markedly slowed when the drug solubility was less than about 3 mg mL\(^{-1}\). Efentakis et al. (2007) showed that although the gross release rate (percent / minute) for theophylline and caffeine were similar, the percentage of caffeine released within the first 50 min was at least double the percentage of theophylline released. They also noted that caffeine caused greater swelling of the matrix tablets than the theophylline. In addition, Varshosaz and Falamarzian (2000) used theobromine as a model hydrophobic drug in their membrane diffusion studies.

2. MATERIALS AND METHODS

2.1. Materials

Low viscosity sodium alginates were obtained from two botanical sources, i.e., *Macrocystis pyrifera* (Sigma Chemical Co., USA) and *Laminaria hyperborae* stipes (Pronova Biomedical, Norway) and are referred to as ALV and LVG respectively. Low methoxy pectin (GENUpectin type LM-104 AS-FS) with 28% esterification and 20% amidation (i.e. LMA) was
the generous gift of CP Kelco (Denmark). Caffeine (CAF), theophylline (TPL) and theobromine (TBR) were obtained from Sigma Chemical Co. (USA) and were sieved to obtain the 150-300 μm fraction. Polyvinylpyrrolidone (average MW 360 000), calcium acetate (sieve fraction 300-355 μm) (Sigma Chemical Co., USA) and microcrystalline cellulose (sieve fraction 45-106 μm) (Avicel PH101, FMC Corp., USA) were used without further purification. All other chemicals were of AR grade and water prepared by reverse osmosis was used in all experiments.

2.2. Solubility measurement

Excess amounts of CAF, TPL or TBR were dispersed in purified water or 0.1 M HCl in triplicated experiments. The samples were shaken in an orbital mixer incubator at 37 °C for 24 h and then allowed to stand for a further 2 h, before the supernatant was filtered and diluted appropriately. Preliminary experiments showed that solubility equilibrium was reached in less than 24 h and that Beer’s Law was obeyed over the range of 0 – 100 mg/L under the conditions specified below (Sriamornsak, 2002). The drug concentration was determined by UV analysis at 270 nm (TPL in 0.1 M HCl), 272nm (CAF and TBR in 0.1M HCl) or 273 nm (TPL, TBR and CAF in water).

2.3. Manufacture of spherical pellets by extrusion-spheronization

One hundred grams of active drug (40%), microcrystalline cellulose (50%) and calcium acetate (10%) were blended for 20 min on a roller mixer (Ratek Instruments, Australia). Fifty grams of 1% w/w polyvinylpyrrolidone were added slowly to the powder blend, which was then mixed until a homogenous, cohesive, plastic mass was obtained. The resulting wet mass was processed in a Model 25 basket extruder (G.B. Caleva, England), with perforations 2 mm in diameter. A uniform extrudate was produced with the extruder set to 30 rpm. Spheronization was undertaken in a Caleva Model 120 spheronizer with a rotating plate of regular crosshatch geometry for 15 min at a speed of 1500 rpm. Pellets were then dried on a tray in an air dryer (Clayson Laboratory Apparatus, Australia) at 50 °C for 24 h.
2.4. Preparation of CaPG coated pellets

Polysaccharide solutions were prepared by dissolving the materials in water with stirring and then leaving them undisturbed overnight in sealed containers to allow the air bubbles to rise. Five grams of pellets, size fraction 1.4–1.7 mm, were dispersed in 300 g of 2% w/w aqueous solution of the polysaccharides by stirring using a 5-cm diameter turbine stirrer at a speed of 400 rpm for 10 min. This allowed the calcium in the pellets to dissolve, diffuse to the surface and cross-link with the polysaccharide to form a water-insoluble calcium gel film around the pellets. Coated pellets were rinsed in 200 mL of water, stirred in 200 mL of 0.34 M CaCl₂ for 5 min, rinsed in 200 mL of water and then stirred in 100 mL of ethanol for 5 min. The coated pellets were filtered, dried at 40 °C for 48 h and stored in glass bottles in a desiccator over silica gel until required.

2.5. Characterization of pellets

2.5.1. Size and shape of uncoated core pellets

The size distribution of uncoated pellets was determined using a nest of sieves (600-2360 μm with 2⁰.₂⁵ progression) and a sieve shaker (Octagon Digital, Endecotts, England) operated for 5 min at a frequency of 50 Hz and an amplitude of 1.4 mm. Image analysis (Image-Pro Plus version 4.1, Media Cybernetics, USA) of core pellets in the size fractions of 1.4–1.7 mm was performed on each batch using at least 200 pellets. Several size and shape parameters were measured or calculated, i.e. Feret diameter, longest diameter, projected area and the projection sphericity. The Feret diameters quoted are based on the mean of 36 diameter measurements using a 5° rotation between each measurement for each pellet. The projection sphericity (PS) was calculated according to Equation 1 (Podczeck et al., 1999) where dₜ is the longest diameter and A is the projected area.
2.5.2. Further characterization of uncoated or coated pellets

The moisture content of uncoated pellets was measured at 105°C with a moisture analyzer (Model MA 40, Sartorius AG, Germany) using about 500 mg of pellets. The mean uncoated pellet weight was determined by individually weighing 50 pellets on an analytical balance (AX200, Shimadzu, Japan) and then calculating the mean and standard deviation.

The mechanical characteristics of the uncoated pellets were determined as described previously (Sriamornsak et al., 2006). In brief, the crushing strength was determined using a universal compression tester (Lloyd Mk 2 with Nexygen 2 software, Lloyd Instruments, UK) with a 500N load cell and operating at a cross-head speed of 5 mm min⁻¹. Individual pellets were strained until fracture occurred. The crushing strength (σₚ) was calculated according to Equation 2,

\[
σₚ = \frac{0.4 \times P_m}{\pi \times r^2}
\]

where \(P_m\) is the maximum load (N) at pellet fracture and \(r\) is the pellet radius (m) (Shipway and Hutchings, 1993). The value of \(r\) for each batch of pellets was estimated as half the maximum diameter as determined by image analysis in section 2.5.1. The means and standard deviations based on 6 replicates are shown.

About 120 mg of the uncoated or coated pellets were accurately weighed in triplicate, added to about 80 mL of 2% w/v trisodium citrate solution (TSC), carefully crushed, stirred for 4 h and then made up to 100 mL with further TSC. The solution was filtered and analyzed by UV spectrophotometry in TSC at 271 nm for TPL and 273 nm for TBR and CAF (Model Cary 1E, Varian Australia Pty. Ltd., Australia). Preliminary experiments showed this protocol was able to
dissolve and analyze the expected quantities of the active agents in the pellets (Sriamornsak, 2002). The encapsulation efficiency (EE) was also calculated according to Equation 3.

\[
EE \ (\%) = \frac{\text{actual drug content (\%)}}{\text{theoretical drug content (\%)}} \times 100 \quad (3)
\]

2.6. In-vitro drug release studies

An automated USP dissolution apparatus type 1 (Model VK7000, Vankel, USA), linked to 6×0.1 cm flow-through UV cells in a UV spectrophotometer (Model Cary 1E, Varian Australia Pty. Ltd., Australia) by a peristaltic pump (Model 17-2300, Vankel, USA) under control of Cary WinUV software (Varian Australia Pty. Ltd., Australia), was used to measure drug release. The temperature was 37 °C, the volume of dissolution media (0.1 M HCl and water) was 1000 mL and the baskets were rotated at 100 rpm. The analytical wavelengths were specified in section 2.2. All dissolution experiments used 250 mg of pellets (equivalent to 100 mg of the active drugs) and were performed in triplicate.

2.7. Statistical analysis

Analysis of variance (ANOVA) and Levene’s test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., USA). Post hoc testing (p<0.05) of the multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene’s test was insignificant or significant respectively.

3. RESULTS AND DISCUSSION

3.1. Drug solubility

Literature values of the pKₐ and the measured solubilities of CAF, TPL and TBR at 37 °C in water and 0.1 M HCl are shown in Table 1. The two media did not cause any statistically significant differences in solubility of the drugs. This was surprising, given that there would be a
large difference in the ionization of the drugs in water compared to 0.1M HCl. However, inspection of Fig. 1 shows that each of the molecules possesses two carbonyl oxygens on the xanthine nucleus and these would allow extensive hydrogen bonding with water. However, there was a significant difference in the solubilities of the three drugs tested in both media; CAF is the most soluble and TBR is the least soluble. The measured solubilities of these drugs at 37 °C were higher than those at 25 °C that are reported in the literature (i.e. about 21.74 g/L for CAF, 8.33 g/L for TPL and 0.50 g/L for TBR) (Budavari, 1996).

3.2. Physical characterization of uncoated pellets

Fig. 2a shows the size distribution (determined by sieve analysis) of uncoated pellets containing CAF, TBR or TPL produced by extrusion and spheronization. The mode size band was 1.4-1.7 mm in each case, although the 1.7-2.0 mm band was only slightly less frequent for all pellets. The 1.4-1.7 mm band of each formulation was further investigated by image analysis to obtain a shape factor and the mean pellet size. The pellet size–frequency distribution of TPL pellets is shown in Fig. 2b and was similar for the other pellets.

The Feret diameter and shape factors of different pellets are given in Table 2. The mean sizes of each type of pellet were not significantly different statistically. As seen from the projection sphericity (where an ideal spherical pellet has a projection sphericity value of 1.0) all pellets were almost spherical. In addition, the uncoated pellets loaded with different drugs had fairly low crushing strengths, and low moisture content, i.e. less than 2% after drying.

3.3. Payload and EE of uncoated and coated pellets

Table 3 shows the actual payload and EE of the drug-loaded pellets. The payload as well as the EE of uncoated pellets of TBR (about 99%) was statistically significantly higher than those of CAF and TPL (each about 90%). The more soluble CAF and TPL could be easily dissolved in the aqueous binding solution and more readily lost during the pellet manufacturing
process, particularly in the wet massing and extrusion steps. The payload in the uncoated TBR pellets was 39.5% compared to about 36.1% for the CAF and TPL.

The payloads and EE of the coated pellets were significantly lower than the uncoated pellets because some drug diffused through the gel into the polysaccharide solution during the coating process. Moreover, the increased total pellet weight resulting from gel film deposition also decreased the percentage payload, which ranged from 23.57 to 33.74% depending on the drug solubility and polysaccharide type. The rank order of the loss of drug followed the order of the solubilities; losses were greatest from CAF and least from TBR. It is likely that substantial amounts of the more soluble CAF and TPL migrated from the core to the external coating solution through the CaPG as it was forming. It is clear that the EE (and payloads) depended on the polysaccharide type; the EE (and payloads) of pellets coated with LMA were significantly lower than those coated with either type of alginate.

3.4. In-vitro drug release studies

The release profiles of the CAF and TBR from uncoated pellets are shown in Fig. 3 together with the release profiles of TPL published previously (Sriamornsak and Kennedy, 2006). In addition, the time to release 50% of the payload (T50) for uncoated and coated pellets in water and 0.1 M HCl are shown in Table 4.

For the uncoated pellets, the release rates of each drug were relatively unaffected by pH of the release media which was in good agreement with a previous report (Yhen et al. 1993) and the values of T50 were similar. This is expected since the solubility of each drug was unaffected by the pH of the medium as shown in Table 1. Despite the overall similarity of the CAF and TPL release profiles, drug release was essentially complete within 40 min for CAF pellets and 60 min for TPL pellets. The difference occurred because the terminal non-linear release phase commenced earlier for TPL than CAF. The drug release from TBR pellets was extremely slow; about 25% of payload was released in 2 h and 80% was released at 24 h in both media. Overall,
the differences in release can be explained by the differences in drug solubility. When the uncoated pellets were exposed to the release medium, the liquid penetrated into the pellets, dissolved the drug to form a saturated solution (as long as undissolved drug is present), and then the drug diffused out of the pellets. So it is reasonable to expect a faster drug release from the pellets loaded with a more soluble drug. Hiorth et al. (2006) also showed very slow release of a poorly soluble model drug (riboflavin) from similar uncoated pellets.

Fig. 4 shows the release profiles of the CAF and TBR from CaPG coated pellets in water and 0.1 M HCl. The corresponding profiles for TPL (Sriamornsak and Kennedy, 2006) are included in Fig. 4 for the purpose of comparison. Overall, the release of the three drugs was about 4-6 times faster from the uncoated pellets compared to pellets with the CaPG coats. These changes are also apparent from the T50 data shown in Table 4. For each of the three drugs, the release was more rapid in the 0.1 M HCl than in water. This is expected since it has been shown CaPG can be converted to physically stable acid gels (Draget et al., 1994; 1996) and that these gels were considerably more permeable than the original CaPG (e.g. Ostberg et al., 1994; Aslani and Kennedy, 1996; Lim and Kennedy, 1996; Sriamornsak and Kennedy, 2006; 2007a,b).

The release of CAF (see Fig. 4a) occurred at a constant rate after the coated pellets contacted the release media; the duration of constant release was about 2-4 h. CAF release occurred immediately and was concurrent with the rehydration of the coat. This was probably due to the dissolution and liberation of drug that was entrapped in the gel film during the coating procedure. Since CAF was the most soluble drug tested, migration of drug into the coat during the coating process and rapid dissolution of that drug during rehydration of the coat is probable.

The release of TPL from CaPG coated pellets was slower than CAF as shown in Figs. 4a and 4b. A key difference between the performance of TPL and CAF was that, in water, the release profiles of the TPL showed a lag-time of 20-40 min (see Fig 4b). This lead to some release profiles displaying a subtle sigmoidal shape, as has been reported previously.
(Sriamornsak et al., 1997; Sriamornsak and Kennedy, 2006). During the initial 2-5% release, the rate of release increased non-linearly as the membrane hydrated, swelled and increased in permeability. This was followed by zero-order release for about 85% of the payload. The duration of constant release of TPL in water was about 4-6 h for LMA- and ALV-coated pellets and was 11-12 h for the LVG-coated pellets. To avoid excessive compression of the abscissa in Fig 4a,b, only the first 10 hours are shown. Finally, a non-linearly decreasing release period was observed as the last 5-10% of the payload was released. This was probably due to the depletion of dissolved drug after the exhaustion of solid drug in the pellets. The lower solubility of TPL (compared to CAF) would be expected to lead to reduced migration of TPL into the coat during the coating process. This would tend to cause the processes of rehydration, drug dissolution and drug diffusion to occur in a more sequential manner, rather than concurrently as appeared to occur for CAF.

The release of TBR from pellets coated with CaPG in 0.1 M HCl and water was very slow by comparison, and as shown in Fig. 4c was incomplete at 24 h. In other experiments, it was clear that release of TBR was incomplete at 60 h (data not shown). It is recognized that the duration of exposure to 0.1 M HCl was not physiological, and it was noted again that release was slower in water than the 0.1M HCl. The release kinetics of the TBR is different to the CAF and TPL, since the curves in Fig. 4c are, after an initial short period of slow release due to the membrane hydration, well described by a first-order relationship as is shown in Fig. 5. It is interesting to note that the use of a different drug (albeit one with much lower solubility) leads to an apparent change in the kinetic order of release through the same membranes. Although this observation is not a major focus of this work, we suggest that it could reflect interactions between the TBR and the CaPG that alter the barrier properties of the membrane. It could also be due to the inability of the dissolution rate of TBR in the restricted fluid space within the pellets.
to maintain a constant concentration of TBR in solution as a driving force to transport through the CaPG membrane.

The results in Fig. 4 show that the slowest release occurred when LVG was used as the coating and for TPL and TBR, the LMA coating allowed the most rapid release. These trends were apparent in both the water and the 0.1 M HCl, although in the acid the difference between the coatings is small. For the CAF, release was slightly more rapid with the ALV coating than the LMA. These trends are expected on the basis of published information. The LVG has a high content of the guluronic acid monomer that is primarily responsible for the formation of calcium cross-links (Moe et al., 1995; Mørch et al., 2006; Li et al., 2007; Sikorski, 2007) and it has been shown that, in comparison to the other CaPG used in this study, the Ca-LVG had the highest calcium content and produced the least permeable gels (Sriamornsak and Kennedy, 2007b). In contrast, the Ca-LMA is known to be stabilized by hydrogen bonding between the amide groups (Alonso-Mougán et al., 2002) and produced highly permeable gels with the lowest calcium content of the CaPG tested (Sriamornsak and Kennedy, 2007b). The ALV has a lower guluronic acid content than LVG, but is known to possess long poly G blocks that do stabilize the gels effectively (Moe et al., 1995) and has a permeability that is intermediate to the LMA and LVG (Sriamornsak and Kennedy, 2007b). The surprising result was that the CAF was released more rapidly through the ALV than the LMA. This may be due to specific molecular interactions between the CAF and the LMA that retard the diffusion of the drug.

The differences in the release of the drugs in water are probably due to (a) differences in the solubility of the drugs that resulted in different concentrations in solution within the pellet, and (b) differences in the mechanism of diffusion. It is likely that differences in the solution concentrations within the pellets will lead to differences in the partitioning of the drugs between the solution state within the pellets and the gel membrane, as well as having a direct influence on
the overall flux through the coats. In addition, differences in the solubility of the drugs are likely to influence the release mechanism, as discussed below.

When the coated pellets were exposed to the medium, the liquid penetrated into the pellets and dissolved the drug to form a saturated solution, from which it partitioned into, and diffused through, the CaPG membrane. In addition, drug that dissolved and was released during the coating process would become entrapped in the membrane and subsequently crystallized during the drying process. It is expected that CAF dissolved most rapidly and achieved the highest solution concentration inside the pellets during rehydration and release. Thacharodi and Rao (1992) suggested that a highly water-soluble drug (propranolol hydrochloride) was transported through microchannels across chitosan membranes. Likewise, the dissolution of CAF crystals in the CaPG membrane would have been likely to form fluid-filled microchannels and may have lead to faster transport through the CaPG films. However, although this explanation of CAF transport through the CaPG films needs further investigation, there have been similar observations in other systems (e.g. El-Malah and Nazzal, 2007). The TPL and TBR with lower solubility than CAF would be expected to be less likely to form microchannels in the CaPG. Therefore, the transport of TPL and TBR through the CaPG is likely to be progressively more dominated by partitioning into, and diffusion through, the membrane itself. Varshosaz and Falamarzian (2001) observed that decreasing drug solubility (comparing aminopyrine, CAF and TBR) increased the partition coefficient, namely about 6-fold for TBR compared to aminopyrine. This suggested that there might be a high affinity between TBR and the hydrogel and perhaps the presence of strong interactions between TBR and the macromolecular segments of the membrane. Although the very slow release of TBR through the CaPG coats is probably largely due to the low solution concentration within the pellet, the TBR could interact with some polysaccharide segments and its transport through the CaPG could be slowed.
4. CONCLUSIONS

It was found that CaPG of either pectin or alginate could be successfully applied by interfacial complexation coating on to pellets loaded with different drugs with similar chemical structures but widely different solubilities. Although the three drugs did not cause marked differences between the mechanical properties of the pellets, the drug with lowest solubility (TBR) had a significantly higher encapsulation efficiency than either the CAF or TPL within the pellets.

The drug release from different uncoated pellets was relatively unaffected by pH of the release medium but depended mainly on drug solubility. Clearly, the drug release behavior was significantly modified in the pellets coated with CaPG, for all drugs tested. Drug release from coated pellets showed different release kinetics for the different drugs. Comparison of the T50 from coated pellets clearly showed that the release of TPL was slower than CAF. The difference in the drug release may be due to the difference in the drug dissolution rate within the core before its partition and transport through the CaPG coat. The transport of CAF may be augmented by the development of microchannels in the coat as CAF dissolves out of the coat. The release of all drugs in coated pellets was about 4 to 6-fold slower than uncoated pellets. The results suggest that the CaPG coating could be used to sustain the release of all drugs tested and work to expand on these studies is continuing.

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LIST OF TABLE CAPTIONS

Table 1  Solubility of caffeine, theophylline and theobromine in water and 0.1 M HCl at 37 °C (n=3).

Table 2  Characteristics of uncoated pellets from 1.4–1.7 mm sieve fraction.

Table 3  Summary of the actual payload and encapsulation efficiency (EE) in different pellets (n=3).

Table 4  Time for 50% drug release of uncoated and coated pellets in 0.1 M HCl and water.
LIST OF FIGURE CAPTIONS

Figure 1  Illustration of the chemical structures of caffeine, theophylline and theobromine.

Figure 2  (a) Size distribution of all uncoated drug-loaded pellets (by sieve analysis, n=4) and (b) pellet size–frequency distribution (by image analysis, n=200) of uncoated pellets of theophylline.

Figure 3  Release profiles of uncoated pellets of different drugs in water and 0.1 M HCl. The means of triplicated data are plotted; the standard deviations are within the point size.

Figure 4  Drug release in water and 0.1 M HCl from calcium polysaccharide gel coated pellets; (a) caffeine, (b) theophylline, and (c) theobromine. The means of triplicated data are plotted; the standard deviations are within the point size.

Figure 5  Plots of the log percentage drug retained in pellets versus time of TBR pellets coated with calcium polysaccharide gels.
Table 1

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<th>Theophylline</th>
<th>Theobromine</th>
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<td><strong>Solubility (g L⁻¹)</strong></td>
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¹ (From Williams, 2002)
Table 2

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<tr>
<td>min</td>
<td>1.28</td>
<td>1.36</td>
<td>1.29</td>
</tr>
<tr>
<td>max</td>
<td>1.73</td>
<td>1.86</td>
<td>1.78</td>
</tr>
<tr>
<td><strong>Projection sphericity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=200; ± S.D.)</td>
<td>0.98 ± 0.06</td>
<td>0.93 ± 0.04</td>
<td>0.93 ± 0.04</td>
</tr>
<tr>
<td>min</td>
<td>0.80</td>
<td>0.81</td>
<td>0.82</td>
</tr>
<tr>
<td>max</td>
<td>1.10</td>
<td>0.97</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>Mean pellet weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg) (n=50; ± S.D.)</td>
<td>2.45 ± 0.46</td>
<td>2.51 ± 0.42</td>
<td>2.58 ± 0.45</td>
</tr>
<tr>
<td><strong>Moisture content</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) (n=3; ± S.D.)</td>
<td>1.83 ± 0.14</td>
<td>1.90 ± 0.28</td>
<td>1.69 ± 0.43</td>
</tr>
<tr>
<td><strong>Mechanical strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MPa) (n=6; ± S.D.)</td>
<td>3.61 ± 0.21</td>
<td>3.32 ± 0.37</td>
<td>3.73 ± 0.23</td>
</tr>
</tbody>
</table>
Table 3

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Payload 1</th>
<th>EE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%w/w) ± S.D.</td>
<td>(%) ± S.D.</td>
</tr>
<tr>
<td><strong>Caffeine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncoated pellets</td>
<td>36.22 ± 0.23</td>
<td>90.55 ± 0.57</td>
</tr>
<tr>
<td>LMA</td>
<td>23.57 ± 0.23</td>
<td>58.92 ± 0.57</td>
</tr>
<tr>
<td>ALV</td>
<td>26.41 ± 0.59</td>
<td>66.02 ± 1.51</td>
</tr>
<tr>
<td>LVG</td>
<td>27.41 ± 0.83</td>
<td>68.52 ± 1.71</td>
</tr>
<tr>
<td><strong>Theophylline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncoated pellets</td>
<td>36.06 ± 0.13</td>
<td>90.16 ± 0.32</td>
</tr>
<tr>
<td>LMA</td>
<td>27.21 ± 0.46</td>
<td>68.03 ± 1.16</td>
</tr>
<tr>
<td>ALV</td>
<td>30.52 ± 0.35</td>
<td>76.29 ± 0.87</td>
</tr>
<tr>
<td>LVG</td>
<td>30.99 ± 0.01</td>
<td>77.48 ± 0.02</td>
</tr>
<tr>
<td><strong>Theobromine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncoated pellets</td>
<td>39.52 ± 0.39</td>
<td>98.79 ± 0.98</td>
</tr>
<tr>
<td>LMA</td>
<td>29.52 ± 0.09</td>
<td>73.80 ± 0.25</td>
</tr>
<tr>
<td>ALV</td>
<td>33.74 ± 0.06</td>
<td>84.34 ± 0.16</td>
</tr>
<tr>
<td>LVG</td>
<td>33.51 ± 0.06</td>
<td>83.76 ± 0.15</td>
</tr>
</tbody>
</table>

1 Payloads are shown as % w/w of active drug in 100 mg of dried pellets.
Table 4

<table>
<thead>
<tr>
<th>Medium</th>
<th>Polysaccharide</th>
<th>T_{50} (min) ± S.D.</th>
<th>Caffeine</th>
<th>Theophylline</th>
<th>Theobromine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 M HCl</td>
<td>Uncoated pellets</td>
<td>12.8 ± 0.1</td>
<td>13.1 ± 0.4</td>
<td>447.9 ± 15.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LMA</td>
<td>55.6 ± 0.6</td>
<td>92.5 ± 1.3</td>
<td>1370.0 ± 20.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALV</td>
<td>44.5 ± 0.1</td>
<td>102.0 ± 2.2</td>
<td>1384.0 ± 35.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVG</td>
<td>48.3 ± 1.2</td>
<td>114.8 ± 0.8</td>
<td>1581.6 ± 54.7</td>
<td></td>
</tr>
<tr>
<td>water</td>
<td>Uncoated pellets</td>
<td>13.1 ± 0.2</td>
<td>14.7 ± 0.1</td>
<td>483.5 ± 16.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LMA</td>
<td>71.7 ± 0.8</td>
<td>128.2 ± 0.6</td>
<td>1470.2 ± 14.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALV</td>
<td>64.3 ± 0.9</td>
<td>221.4 ± 4.8</td>
<td>1722.5 ± 35.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVG</td>
<td>102.8 ± 1.5</td>
<td>387.2 ± 2.3</td>
<td>2309.0 ± 94.4</td>
<td></td>
</tr>
</tbody>
</table>
Caffeine  
(1,3,7-trimethylxanthine)  
Theophylline  
(1,3-dimethylxanthine)  
Theobromine  
(3,7-dimethylxanthine)

Figure 1
Figure 2
Figure 3
Figure 4

(a)

(b)

(c)
Figure 5