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Development of polysaccharide gel coated pellets for oral administration 1. Physico-mechanical properties

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Abstract

Spherical pellets containing theophylline, calcium acetate and microcrystalline cellulose were extruded and spheronized, before being coated with six different pectins or alginates by interfacial complexation. The aim of this study was to discover the effect of the coatings on physico-mechanical properties that will be crucial in determining the pellets' utility as sustained release systems. An insoluble, smooth and uniformly thick coat of calcium polysaccharide was formed around the core pellets. A factorial experiment was designed to investigate the effect of pellet size and polysaccharide type and concentration on the entrapment efficiency, mechanical properties and other physical characteristics. Coated pellets were observed by scanning electron microscopy and, depending on the particular polysaccharide used, the dry coats were found to be 30–80 μm thick. The size of pellet, the type and concentration of polysaccharide influenced the yield of theophylline in the coated pellets. Although the mechanical properties of the pellets were improved by applying any of the gel coats, use of an alginate with a high content of guluronic acid or an amidated pectin coating gave the best results. This is probably because both of these have significant potential to form very stable cross-links within the gel coats.

Keywords: Extrusion and spheronization; Alginate; Pectin; Polysaccharide coatings; Physico-chemical properties of coated spheres

1. Introduction

Oral controlled release dose-forms have gained popularity in recent years. They broadly fall into two categories: single-unit and multiple-unit dose-forms. The single-unit dose-forms are either matrix tablets or coated tablets that do not disintegrate in the gastrointestinal tract. The multiple-unit dose-forms consist of pellets or microencapsulated drug contained in a capsule or a tablet. The various methods and approaches that have been used in the formulation of multiple-unit dose-forms have been thoroughly discussed in many standard reference works (e.g. Ghebre-Sellassie, 1994).

Multiple-unit systems are of great interest to the pharmaceutical industry for a variety of reasons. Palletized products not only offer flexibility in dose-form design and development, but are also used to improve the safety and efficacy of bioactive agents. However, the single most important factor responsible for the proliferation of pellets is the widespread use of controlled release technologies (Ghebre-Sellassie, 1989a). It has been known for many years that pellets containing the active ingredient are administered *in vivo* in the form of capsules or disintegrating tablets, offer significant therapeutic advantages over single unit dose-forms (Bechgaard and Nielsen, 1978). Because pellets disperse freely in the gastrointestinal tract, they often maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects. Pellets show other benefits, such as a gradual decrease in the amount present in the stomach (Davis et al., 1986), less local irritation, longer and more predictable transit times in the gastrointestinal tract, lower intersubject variation of plasma concentrations of the drug, and less immobilization near restrictions in the gastrointestinal tract (Ghebre-Sellassie, 1989a). Recently, Sinha et al. (2005) have summarized the many biopharmaceutical and physico-chemical advantages of using small spherical pellets as the basis of a drug delivery system.

Coating of pellets with an insoluble barrier membrane offers a reliable method of regulating the drug release. The diffusion-controlled interfacial complexation technique is a

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coating process providing defect-free, uniform coating on solid units (Bhagat et al. 1990; Sriamornsak et al., 1997a,b). In the present study, two anionic polysaccharides, (sodium alginates and low methoxy pectins), that can react with divalent cations (e.g. calcium ions) to form cross-linked and water-insoluble gels, have been investigated.

Spherical theophylline pellets, that also contain microcrystalline cellulose (MCC) and calcium acetate, were prepared using an extrusion-spheronization method and then coated with various polysaccharides. Theophylline has been widely used as a model drug, especially for products intended to display sustained release profiles. There are many features that informed our choice of theophylline, namely, ready availability, relatively low cost, ease of assay, chemical stability and the therapeutic relevance of a sustained release dose-form. MCC has been very widely used in the formation of extruded and spheronized spheres since the early studies of O'Connor, Schwartz and coworkers (e.g. O'Connor et al., 1984). It has been shown that MCC is able to be formed into spheroids over a wide range of drug:MCC ratios, largely due to the favorable plastic rheological characteristics of the MCC/drug/water pastes that are formed. Pellets formed with MCC have been proven many times (since those early studies) to be dense and spherical, to possess a narrow size distribution and to display good release characteristics for active drugs (e.g. Sinha et al., 2005).

The aims of this study were to produce spherical pellets within the approximate size range of 1–2 mm and to begin to explore the utility of calcium alginate or calcium pectinate coats on those pellets as a means to achieve a sustained release profile of the active drug, theophylline. It was considered important to produce this size range, since it has been known for a number of years that spherical pellets less than 2 mm in diameter are emptied from the stomach by zero-order kinetics and are delivered to the intestine in significant quantities within 30–60 min (e.g. Parr et al., 1990). A multi-level factorial design was applied to determine the effect of the size of pellets, type and concentration of polysaccharides on the pellet characteristics. The characteristics of the uncoated and coated pellets, namely payload, entrapment efficiency, moisture content, size and shape of uncoated pellets and morphology of the uncoated and coated pellets as well as mechanical properties of uncoated and coated pellets, were investigated.

2. Materials and methods

2.1. Materials

Low and medium viscosity sodium alginates (ALV and AMV, respectively) obtained from *Macrocystis pyrifera* were purchased from Sigma Chemical Company (USA). Low viscosity sodium alginates obtained from *Laminaria hyperborae* leaves and stipes (i.e. LVM and LVG, respectively) were purchased from Pronova Biomedical (Norway). Low methoxy pectin with 28% esterification was obtained from two sources. A commercial pectin (LMA) with 20% amidation (GENUpectin type LM-104 AS-FS) was the generous gift of CP Kelco (Denmark). A potassium salt of esterified pectin from citrus fruit (LMC) was purchased from Sigma Chemical Company (USA). Theophylline (150–300 μm), polyvinylpyrrolidone (i.e. PVP, average molecular weight 360,000), calcium acetate (300–355 μm) (Sigma Chemical Company) and microcrystalline cellulose (i.e. MCC, 45–106 μm) (Avicel PH101, FMC Corporation, USA) were used as received. All other chemicals were of AR grade and water prepared by reverse osmosis was used in all experiments.

2.2. Manufacture of spherical pellets by extrusion-spheronization

Forty grams of theophylline, 50 g microcrystalline cellulose and 10 g calcium acetate were blended for 20 min on a roller mixer (Ratek Instruments, Australia). Fifty grams of a 1% (w/w) aqueous solution of polyvinylpyrrolidone were added slowly to the powder blend, and were mixed until a homogenous, cohesive, plastic mass was obtained. The resulting wet mass was extruded at 30 rpm (Model 25, G.B. Caleva, England), through perforations 1 or 2 mm in diameter. Spheronization was performed 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.

2.3. Characterization of pellets

2.3.1. Pellet size and shape

The particle size distribution of uncoated pellets was determined by sieving (600–2360 μm with $2^{0.25}$ progression) on a sieve shaker (Octagon Digital, Endecotts, England) for 5 min at a frequency of 50 Hz and with an amplitude of 1 mm. Image analysis was performed on two size fractions of core pellets, i.e. 0.85–1.00 mm (from 1-mm screen) and 1.40–1.70 mm (from 2-mm screen). The pellets were spread over a flat surface by spatula and a digital image was collected. Under the same optical conditions, an image of a linear scale was used to calibrate the image analysis software, Image-Pro Plus v. 4.1 (Media Cybernetics, USA). The data taken from the pellet images were the Feret diameter, longest diameter and projected area (A).

The Feret diameter of a pellet is defined as the average of 36 caliper measurements around the particle employing a 5° angle of rotation. The projection sphericity (PS) of a pellet was calculated according to

$$\mathrm{PS} = \frac{4A}{\pi d_{\mathrm{L}}^2} \tag{1}$$

where d_{L} is the longest caliper distance observed when tracing around the particle (Podczeck et al., 1999). A perfect sphere will have PS = 1.

2.3.2. Pore size and density determination

The pore volume and pore diameter were measured by mercury intrusion with a 400 mg sample of uncoated pellets using an Autopore 9220 II porosimeter (Micromeritics Instrument Corporation, USA). The measured total porosity values were determined from the penetration volume at pressures up to

414 MPa. True density of uncoated pellets was measured by helium pycnometry (AccuPyc 1330, Micromeritics Instrument Corporation, USA).

2.3.3. Content and release kinetics of calcium from pellets

The amount of calcium in the uncoated pellets was determined by complexometric titration. About 500 mg of uncoated pellets were accurately weighed, crushed, shaken and extracted into 250 mL of deionized water. A 10 mL sample was mixed with 1 mL of 28% ammonia solution and titrated with standardized sodium EDTA, using one indicator buffer tablet (Merck, Germany). The determination was performed in triplicate. Release of calcium from the uncoated pellets was also investigated. About 500 mg of the uncoated pellets were accurately weighed and added into 300 mL of deionized water. The temperature was 25 °C and the stirring rate was 400 rpm. At specific times, 10 mL of samples were manually collected, replaced with fresh medium and the calcium released was titrated complexometrically.

2.3.4. Determination of drug payload and moisture content in pellets

Suitable weights of pellets were suspended in 2% (w/v) trisodium citrate (TSC) solution to dissolve the gel coats before the pellets were crushed to release the payload. The solution was filtered and analyzed by UV spectrophotometry in TSC at 271 nm (Model Cary 1E, Varian Australia Pty. Ltd., Australia). The entrapment efficiency (EE) was calculated with the following equation:

$$\text{EE}\,(\%) = \frac{\text{actual drug content}\,(\%)}{\text{theoretical drug content}\,(\%)} \times 100 \quad (2)$$

The moisture content of uncoated and coated pellets was measured at 105 °C with a moisture analyzer (Model MA 40, Sartorius AG, Germany) using about 500 mg of uncoated pellets and 150 mg of coated pellets.

2.3.5. Mechanical properties of pellets

The crushing strength of the pellets at 25 °C was determined using a universal compression tester (Lloyd Mk2 operating with Nexygen 2 software, Lloyd Instruments, UK), with a 500 N load cell operating at a cross-head speed of 5 mm/min. Pellets were strained until failure occurred.

The maximum crushing strength (σ_m) is calculated from the maximum applied load and the cross-sectional area of a pellet as described in the following equation:

$$\sigma_m = \frac{0.4 P_m}{\pi r^2} \quad (3)$$

where P_m is the maximum load at failure (N) and r is the radius of the spherical pellet (m) (Shipway and Hutchings, 1993).

The normalized work of failure (NWF) was calculated according to the following equation:

$$\text{NWF} = \frac{0.4}{\pi r^2} \int P\,\mathrm{d}x \quad (4)$$

where r is the pellet radius (m), P the load applied (N) and dx is the deflection (m) (Davies and Newton, 1995). The integral of $P\,\mathrm{d}x$ is the area under the acquired load–deflection curves and was calculated by the Trapezoidal rule. The load–deflection data, for uncoated and coated pellets, were converted to stress–strain curves. Stress was calculated by dividing the applied load by the cross-sectional area. Strain was calculated as a percentage of the deformation divided by the original diameter. The elastic modulus is defined as the ratio of stress to strain and can be calculated from the slope of the initial linear portion (i.e. between 0.05 and 0.25%) of stress–strain curves (Aulton, 1995).

2.3.6. Morphology of pellets

Morphological examination of the surface and internal structure of uncoated and coated pellets was carried out using a scanning electron microscope (Hitachi S2250-N, Japan) at an accelerating voltage of 10 keV. For examination of the internal structure of the pellets, they were cut in half with a steel blade.

2.4. Preparation of calcium polysaccharide gel coated pellets

Five grams of pellets in the size fractions 0.85–1.00 and 1.40–1.70 mm, were dispersed in 300 g of 1–4% (w/w) aqueous solutions of the six 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 pellet. Coated pellets were rinsed in water, stirred in 0.34 M $CaCl_2$ for 5 min, quickly rinsed in water again and then stirred in ethanol for 5 min. The coated pellets were filtered, dried at 40 °C for 48 h and stored in glass bottles in a desiccator.

Table 1
Summary of the experimental design used

Factor	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Pellet size (mm)	0.85–1.00	1.40–1.70	NA[a]	NA	NA	NA
Polysaccharide type[b]	LMC	LMA	ALV	AMV	LVM	LVG
Polysaccharide concentration (%)	1	2	3	4	NA	NA

[a] Not applicable.
[b] LMC, low methoxy pectin, conventional (from Sigma Chemical Co., USA); LMA, low methoxy pectin, amidated (from CP Kelco, Denmark); ALV, low viscosity sodium alginate with $F_G = 0.36$ (from Sigma Chemical Co., USA); AMV, medium viscosity sodium alginate with $F_G = 0.31$ (from Sigma Chemical Co., USA); LVM, low viscosity sodium alginate with $F_G = 0.38$ (from Pronova Biomedical, Norway); LVG, low viscosity sodium alginate with $F_G = 0.73$ (from Pronova Biomedical, Norway).

2.5. Statistical design and analysis

The experimental design for testing the effect of pellet size, polysaccharide type and concentration was a complete $2 \times 6 \times 2$ multi-level factorial design as shown in Table 1. Analysis of variance (ANOVA) was performed using SPSS version 10.0 for Windows (SPSS Inc., USA). An *a priori* Scheffé test was applied to the experimental values at a significance level of $p < 0.05$.

3. Results and discussion

3.1. Manufacture of spherical pellets

Stable spherical pellets containing theophylline, MCC, calcium acetate and PVP were produced by extrusion and spheronization. Sinha et al. (2005) studied a range of grades of MCC, and showed that the grade of MCC used in our study (i.e. Avicel PH101) produced the best pellets. Variables that may influence the quality of the final pellets, including the type and concentration of binder, type of extruder, extrusion speed and temperature, spheronization speed, and time as well as drying method, were kept constant. In our preliminary studies, it was shown that the amount and concentration of binder affected the appearance of the resulting pellets. Increasing the volume of binder solution, increased the mean size of pellets but decreased the yield in the desirable pellet size range. When lower amounts of binder solution were used, spherical pellets were not obtained. The use of an excess amount of binder gave rod-shaped pellets. The addition of 50 g of 1%PVP to 100 g of powder blend gave an optimum yield of spherical pellets in the required size ranges. The spheronization speed and spheronization time were also optimized to achieve good quality (round and smooth) pellets in the preliminary study. The pellets obtained from the higher spheronization speeds were more spherical than those from the lower speeds, as was previously demonstrated (Umprayn et al., 1999).

3.2. Characterization of uncoated pellets

Pellets made with the 1 mm screen gave a narrower particle size distribution (mode = 0.85–1.00 mm) while those made with the 2 mm screen had a broader distribution and a mode of 1.40–1.70 mm. Image analysis was performed on the pellets in these size bands that are called the small and large pellets. Within each band, the pellet sizes were normally distributed (data not shown) and their mean Feret diameters and PS are given in Table 2. The roundness of the pellets is important for improved coating and flowability (Baert et al., 1993). The results in Table 2 show that the large pellets were slightly more spherical than the small pellets.

Table 3
Summary of physico-chemical characteristics of uncoated pellets

Properties	Small pellets	Large pellets
Average weight ($n = 50$) (mg/pellet)	0.80 ± 0.17	2.51 ± 0.42
Porosity (%)	20.27	21.28
Average pore diameter (μm)	0.0140	0.0133
Median pore diameter (μm)	0.0061	0.0073
True density (g/cm^3)	1.60	1.45
Moisture content (%)	1.70 ± 0.04	1.90 ± 0.28
Calcium content (mg/g)	27.12 ± 0.94	26.76 ± 0.91
Theophylline payload (%)	36.26 ± 0.01	36.06 ± 0.14
Entrapment efficiency (%)	90.64 ± 0.02	90.16 ± 0.32

The porosity, density and calcium content of small and large uncoated pellets are given in Table 3. Calcium was released rapidly from the uncoated pellets; about 85% of the calcium was released in 10 min (data not shown). However, this would be expected to decrease during the coating process, since the viscous gel coating deposited on the surface would slow subsequent diffusion of calcium ions.

The actual payloads and EE of small and large uncoated pellets are shown in Table 3. The payload is defined as the percentage (w/w) content of theophylline in 100 mg of dry coated pellets. The payload of both small and large pellets was about 36% and EE was about 90%. The drug lost during the pellet manufacturing process, particularly in the wet massing and extrusion steps and weight of residual water, decreased the EE of the pellets.

3.3. Characterization of coated pellets

When the pellets were immersed into an aqueous solution of polysaccharide, a highly hydrated gel coat developed around the pellets, as a result of the cross-linking reaction between polysaccharide in solution and the free calcium acetate diffusing from the pellets. Although other cations (e.g. zinc) can be used for cross-linking of alginate (e.g. Aslani and Kennedy, 1996), calcium is the most commonly chosen ion. The cross-linking reaction has been traditionally described in terms of an 'egg-box model' for the cooperative binding of two or more chains (Grant et al., 1973). Gel formation has been demonstrated to result from a specific interaction between (calcium) cations and blocks of galacturonate and guluronate (G) residues in pectin and alginate, respectively (Kohn, 1975). However molecular modeling studies (Braccini and Perez, 2001) have suggested that (for galacturonate) the strong "egg-box" associations are supplemented by weaker associations between the chains. Furthermore, it has

Table 2
Pellet size and projection sphericity of uncoated pellets using image analysis ($n = 200$)

Shape factor	Small pellets	Large pellets
Sieve fraction	0.85–1.00 mm	1.40–1.70 mm
Mean Feret diameter	1.039 ± 0.099 mm, min. 0.858 mm, max. 1.334 mm	1.583 ± 0.104 mm, min. 1.356 mm, max. 1.858 mm
Projection sphericity (PS)	0.827 ± 0.065, min. 0.683, max. 0.948	0.92 ± 0.038, min. 0.812, max. 0.965

recently been proposed that associations between GG and MG blocks can occur in alginate gels (Donati et al., 2005).

Immediately after deposition, the coats were flexible, with a pale yellow translucent appearance for pectin and a more transparent appearance for alginate. Pellets coated with high G-content alginate (i.e. LVG) gave a clearer and more transparent coat than any of the other alginates. The coated pellets were treated with calcium chloride and absolute ethanol to make the coats more robust and easily dried, respectively. This is akin to the aqueous calcium chloride methanol bath used in making alginate-chitosan hybrid fibers (Iwasaki et al., 2004).

Table 4 shows the payload and EE of small and large pellets coated with different polysaccharides at different concentrations. The content of both small and large uncoated pellets was about 36% but the payload of the coated pellets was lower because theophylline diffused through the gel coating as it formed. Statistically, the payload and EE, were significantly increased by using large pellets, as noted previously (Sriamornsak et al., 1997a). This is probably caused by the relatively greater surface area of the small pellets combined with the longer diffusional pathlength in the large pellets. In general, a decrease in payload and EE was observed among pellets coated with increasing concentration of polysaccharides. The effect of increased concentration on the reduction of payload and EE depended on polysaccharide type, being greater with pectin and small pellets. Although the payload and EE of pellets coated with ALV, AMV and LVM were not significantly different to each other, they were significantly lower than those coated with LVG.

Uncoated pellets had lower moisture content (1.69 and 1.90% for small and large uncoated pellets, respectively) than coated pellets (2.11–6.92%). It is probable that most of the additional moisture content was in the coats. In general, moisture would plasticize the "dry" film coat making it softer and more flexible. Statistically, there was a significant increase in moisture content of coated pellets, as the pellet size decreased, but neither the polysaccharide type nor concentration affected moisture content.

3.4. Morphology of the uncoated and coated pellets

Figs. 1 and 2 show electron micrographs of uncoated and coated pellets. Fig. 1(a and b) shows the external and internal appearance of large uncoated pellets; the appearance of the small pellets was identical to the large pellets. The small density differences between small and large pellets (see Table 2) were not perceptible. The pellets are approximately spherical with a slightly rough surface and have a porous structure. Fig. 1(c) shows the surface appearance of the pellets coated with 2%ALV. The surface structure of all coated pellets appeared the same irrespective of polysaccharide type or concentration. Fig. 2 shows the cross-sections of small and large pellets coated with 1 and 2%ALV. The dried ALV coats were smooth, 30–40 μm thick and the thickness of the alginate coat was independent of the pellet size and concentration of coating solution. Similar results were observed for other alginates (i.e. AMV, LVM and LVG). The thickness of the dried pectin coats (i.e. LMC and LMA) was almost the same for the small and large pellets. However, the ratio of coat thickness to pellet size for small pellets was greater than that of large pellets. The thickness of pectin coats increased from 40 to 80 μm with increased pectin concentration.

3.5. Mechanical properties of uncoated and coated pellets

The capacity of a film coat to afford physical protection to a dose-form, depends on its ability to be durable and to resist chipping and cracking during handling (Aulton, 1995). In order to

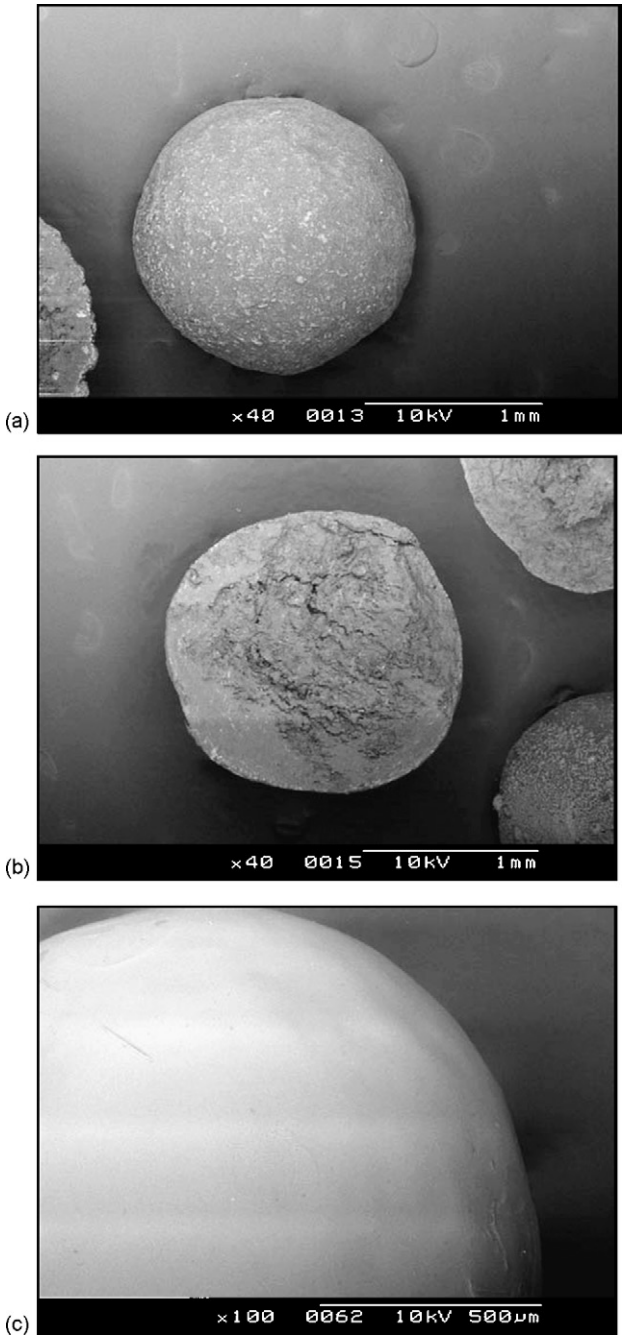

Fig. 1. Scanning electron micrographs of (a) the external and (b) the internal structure of large uncoated pellets, and (c) the external structure of the large pellets coated with 2%ALV. Magnifications and scale bars are shown on the individual photographs.

Table 4
Summary of the theophylline payload and entrapment efficiency (EE) in the uncoated and coated pellets ($n = 3$)

Formulation	Small pellets		Large pellets	
	Payload (%, w/w) ± S.D.	EE (%) ± S.D.	Payload (%, w/w) ± S.D.	EE (%) ± S.D.
Uncoated	36.26 ± 0.01	90.64 ± 0.01	36.06 ± 0.13	90.16 ± 0.31
1%LMC	26.85 ± 0.25	67.12 ± 0.62	29.80 ± 0.05	74.51 ± 0.13
2%LMC	25.72 ± 0.01	64.31 ± 0.03	28.28 ± 0.08	70.70 ± 0.21
1%LMA	24.15 ± 0.08	60.39 ± 0.19	28.06 ± 0.22	70.16 ± 0.55
2%LMA	23.02 ± 0.26	57.56 ± 0.64	27.21 ± 0.46	68.03 ± 1.16
3%LMA	22.44 ± 0.21	56.09 ± 0.52	25.56 ± 0.14	63.90 ± 0.35
4%LMA	21.81 ± 0.55	54.52 ± 1.38	24.10 ± 0.40	60.25 ± 1.01
1%ALV	27.32 ± 0.02	68.31 ± 0.04	30.95 ± 0.39	77.37 ± 0.98
2%ALV	25.83 ± 0.22	64.58 ± 0.54	30.52 ± 0.35	76.29 ± 0.87
1%AMV	26.74 ± 0.21	66.86 ± 0.52	30.27 ± 0.72	75.68 ± 1.81
2%AMV	25.97 ± 0.24	64.93 ± 0.60	29.78 ± 0.23	74.44 ± 0.58
1%LVM	27.03 ± 0.02	67.56 ± 0.04	31.17 ± 0.53	77.93 ± 1.31
2%LVM	26.09 ± 0.26	65.23 ± 0.65	30.03 ± 0.04	75.09 ± 0.11
1%LVG	29.09 ± 0.66	72.72 ± 1.65	31.41 ± 0.09	78.52 ± 0.22
2%LVG	27.88 ± 0.33	69.71 ± 0.83	30.99 ± 0.01	77.48 ± 0.02

investigate the mechanical properties of the pellets, compression tests were performed. A typical plot of applied load versus displacement for uncoated and coated pellets subjected to rupture is shown in Fig. 3. The parameters of most significance are the displacement of the probe from initial contact to rupture of the pellet, area under the curve and the peak load. From this data, apparent tensile strength, normalized work of failure and the elastic modulus were calculated. The theory behind the computation of these parameters is well documented (e.g. Davies and Newton, 1995).

3.5.1. Crushing strength

During spheronization, as water evaporates, dissolved substances in the pellets may migrate to the surface and form a crust that provides a barrier to further moisture transfer, thereby trapping some water in the pellets. The low levels of trapped water

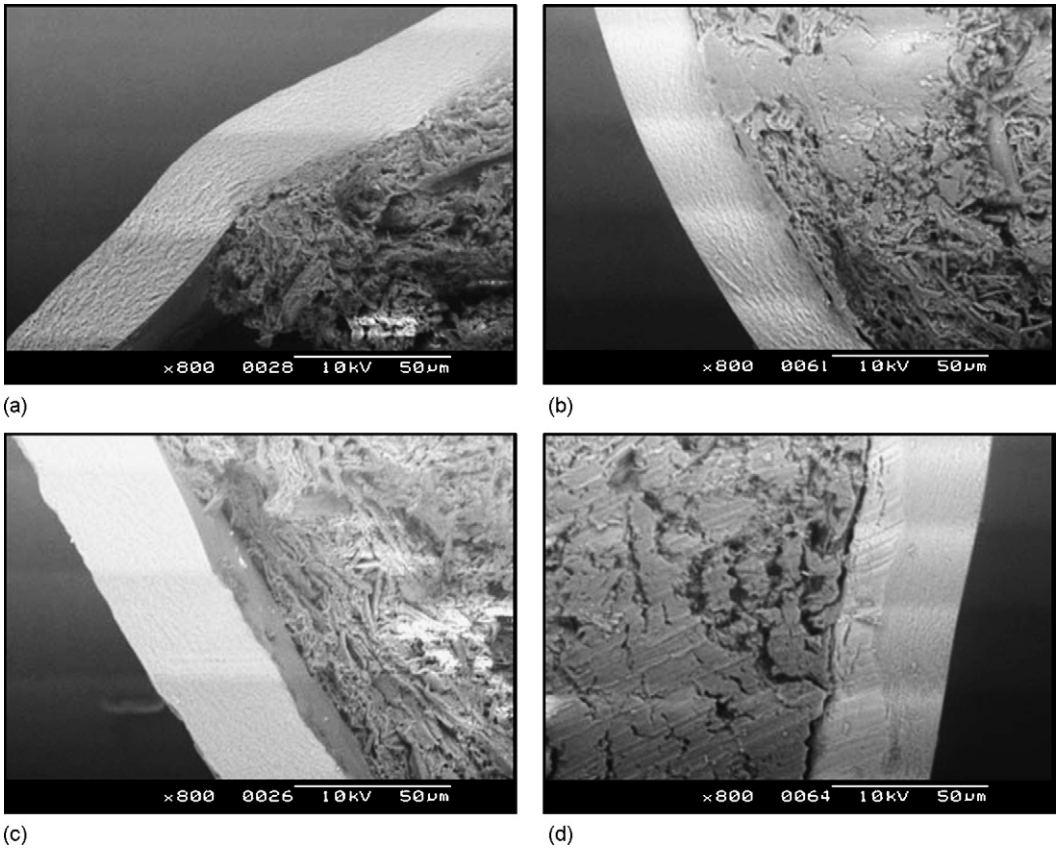

Fig. 2. Scanning electron micrographs of the cross-section of small pellets coated with (a) 1%ALV and (b) 2%ALV; large pellets coated with (c) 1%ALV and (d) 2%ALV. Magnifications and scale bars are shown on the individual photographs.

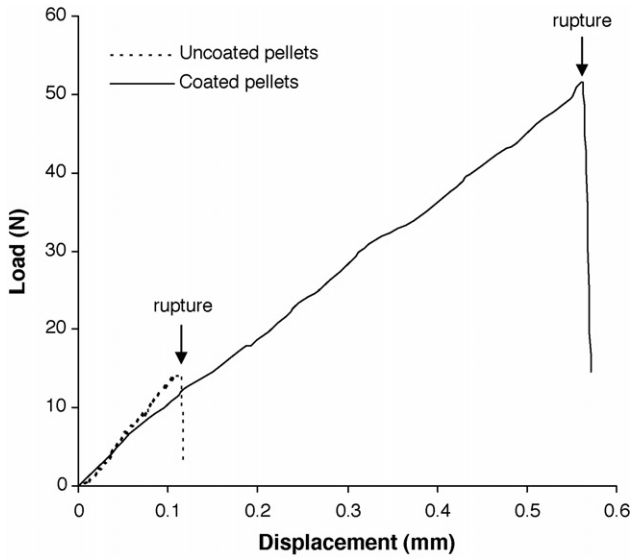

Fig. 3. Typical plot of load vs. displacement data for large uncoated and coated pellets (1%ALV) subjected to rupture. The height of the peak is the load required to rupture the pellet.

makes a significant contribution to the strength of the pellet by forming liquid bridges (Ghebre-Sellassie, 1989b). On drying, however, a porous pellet with reduced mechanical strength may be produced.

Dyer et al. (1994) suggested that the resistance of individual pellets to crushing is related to the cohesive and adhesive properties of the excipients, their size and shape as well as other properties that are specific to the manufacturing process. Fig. 4 shows the effect of pellet size, polysaccharide type and concentration on the crushing strength (CS) of pellets. Although the mean CS of small uncoated pellets was higher than that of the large pellets, the difference was statistically insignificant. The higher density of small pellets (see Table 3) may contribute to the difference between the CS of small and large pellets. The application of any coating increased the CS. Although the CS of the coated pellets was the combined result of the core pellet and its coat, the existence of a single peak in the load/displacement curves for coated pellets suggested that the coat and core failed simultaneously. It has been suggested that this indicates that the coated pellets have a high core/coat adhesion (Fell et al., 1979). The coat may increase the apparent CS by acting as a padding material during the test or by acting as an envelope, that has enough intrinsic strength and elasticity to hold a broken pellet together (Fell et al., 1979; Stanley et al., 1981).

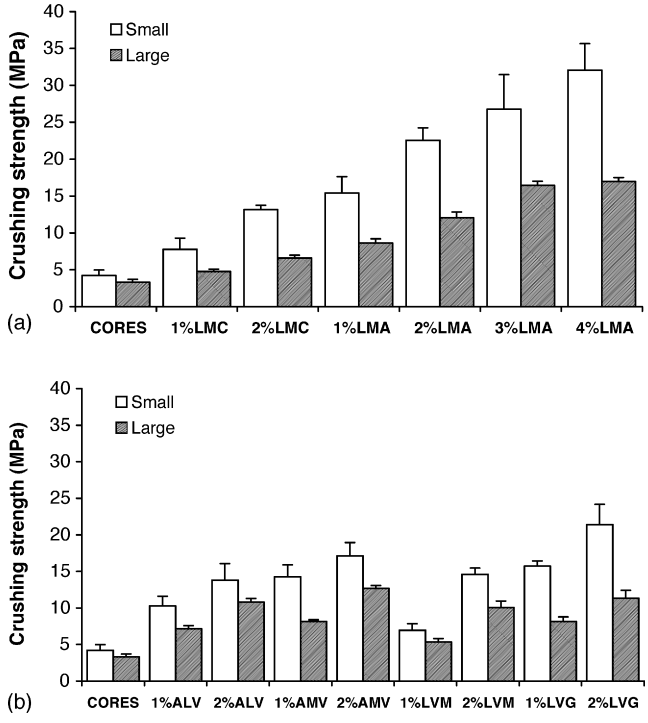

Fig. 4. Crushing strength of uncoated pellets and pellets coated with (a) pectin and (b) alginate. Means and standard deviations of at least six replicates are shown.

Statistically, the CS of small coated pellets was significantly higher than the large coated pellets, irrespective of the coating. This may be due to the density differences of the core pellets or due to the relatively thicker coat on the small coated pellets. The effect of polysaccharide type and concentration is the same for both small and large coated pellets. All increases in polysaccharide concentration resulted in an increased mean CS, but not increases were statistically significant. The rank order of the mean CS of the uncoated pellets (UC) and pellets coated with 1 or 2% polysaccharide is shown below:

CS :

$$\mathrm{UC} < \{\mathrm{LMC} \approx \mathrm{LVM} \approx \mathrm{ALV}\} < \{\mathrm{AMV} \approx \mathrm{LVG}\} < \mathrm{LMA}$$

The < symbol implies a statistically significant difference and the polysaccharides listed within { } did not display a statistically significant difference. Amidated pectin (LMA) produced stronger coated pellets than non-amidated pectin (LMC). This agrees with the observation that increased amidation of calcium pectinate gels increased their tensile strength (Kim et al., 1978). For the pellets coated with alginate, it appears that high-G alginate (LVG) with greater potential for cross-linking is stronger than low-G (LVM). The difference between ALV and AMV may simply be due to molecular weight differences. Although AMV has a similar overall mannuronic/guluronic molar ratio to ALV, the AMV has fewer, but large guluronic blocks (Moe et al., 1995). This means that AMV may form more stable cross-links than ALV.

3.5.2. *Normalized work of failure (NWF)*

The CS does not fully reflect the cohesion of the pellet and the toughness of the coat. These may be better represented by the NWF. Coated pellets with high NWF deformed plastically under compression, thus requiring a relatively large platen displacement to produce failure while uncoated pellets, that are more brittle, require only a small displacement to produce failure. The NWF of uncoated and coated pellets are shown in Fig. 5.

Although there was no significant difference between the NWF of small and large uncoated pellets, the application of any coating increased the NWF. However, the NWF of the small and large coated pellets were not significantly different. Although

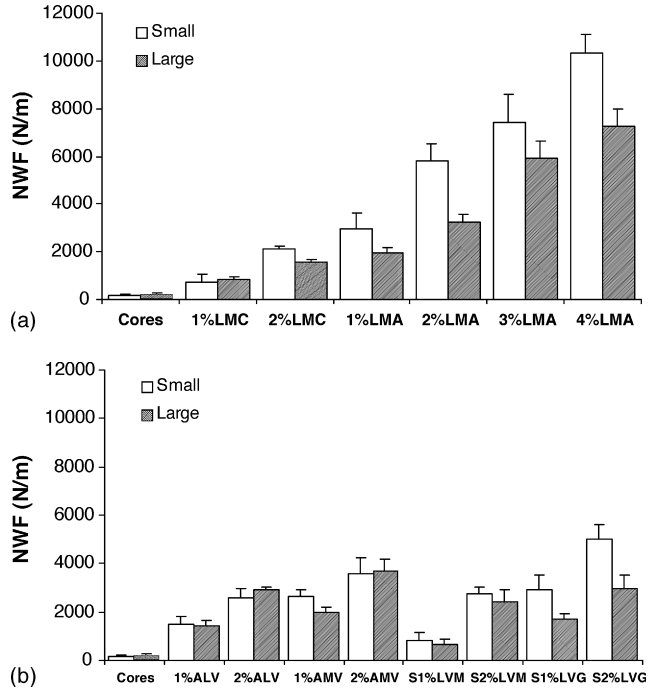

Fig. 5. Normalised work of failure (NWF) of uncoated pellets and pellets coated with (a) pectin and (b) alginate. Means and standard deviations of at least six replicates are shown.

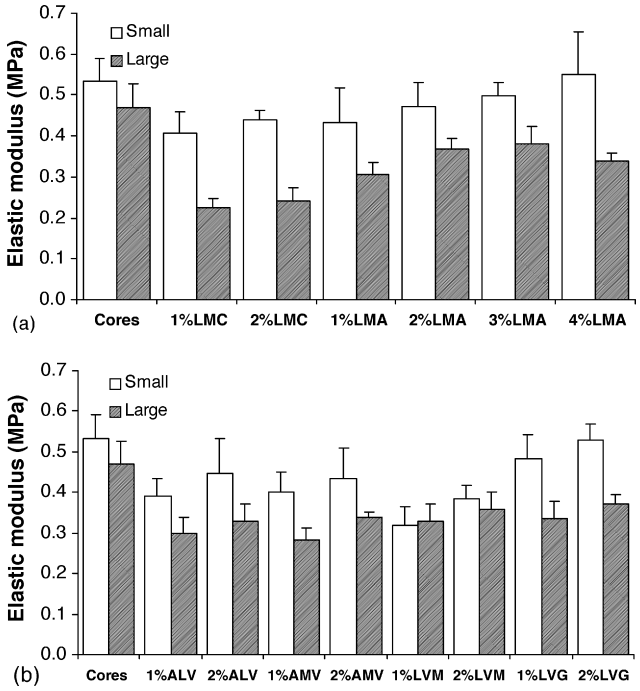

Fig. 6. Elastic modulus of uncoated pellets and pellets coated with (a) pectin and (b) alginate. Means and standard deviations of at least six replicates are shown.

there were notable exceptions (i.e. LMA and LVG) pellet size did not generally influence the NWF of coated pellets. The effect of increasing polysaccharide concentration was more obvious especially for LMA and LVG. The rank order of the means of NWF of pellets coated with different polysaccharides (1 or 2%) is shown below:

NWF :

$$\text{UC} < \{\text{LMC} \approx \text{LVM}\} < \text{ALV} < \{\text{AMV} \approx \text{LVG}\} < \text{LMA}$$

The NWF of pellets coated with LMA was significantly higher than pellets coated with LMC; this suggests that amidation yields a more elastic gel. The NWF of pellets coated with AMV and LVG were not significantly different, but were significantly higher than the pellets coated with ALV and LVM. This may be explained by the greater probability of formation of stable calcium cross-links in LVG or AMV. Both ALV and LVM have short guluronate blocks and less chance of forming stable cross-links.

3.5.3. Elastic modulus

The initial slope of stress–strain curves derived from data (such as those shown in Fig. 3) is the elastic modulus (EM). High values of EM imply greater resistance to deformation. The EM for uncoated and coated pellets are shown in Fig. 6. The EM of small and large uncoated pellets were not significantly different and were relatively high. Uncoated pellets were rather brittle since they had low CS and high EM. All coated pellets had higher CS and lower EM than uncoated pellets and they were considered to be stronger or tougher. Increasing the concentration of polysaccharide did not significantly affect EM and this suggested that the polysaccharide concentration did not significantly increase the stiffness of the coated pellets. The rank order of the EM means of all pellets is given below:

EM :

$$\{\text{LMC} \approx \text{LVM} \approx \text{ALV} \approx \text{AMV}\} < \{\text{LMA} \approx \text{LVG}\} < \text{UC}$$

Statistically, the mean EM of coated pellets could be divided into two groups. The LVG and LMA (that from discussions above are the most likely to have very stable cross-links) were greater than all the other coatings. The EM of all the coated pellets were significantly lower than the uncoated pellets. This is in agreement with Stanley et al. (1981) who suggested that the application of flexible polymeric film coats generally give a lower EM than the uncoated tablet.

4. Conclusions

Spherical pellets containing theophylline, calcium acetate and microcrystalline cellulose were produced by extrusion and spheronization. The pellet size and shape, theophylline and calcium content, moisture content, porosity and density of selected size fractions of pellets were characterized. The pellets were coated with six different pectins or alginates by interfacial complexation. The coats on the pellets were observed by scanning electron microscopy and found to be 30–80 μm thick when dry. The size of pellet, the type and concentration of polysaccharide all influenced the yield of theophylline in the coated pellets. The uncoated pellets were rather brittle since they possessed a low compression strength and high elastic modulus. Although these mechanical properties of the pellets were improved by

applying any of the gel coats, the best coatings were an alginate with a high content of guluronic acid or amidated pectin, both of which have the potential to form very stable cross-links within the gel coats. From the perspective of developing a robust delivery system, a reduction in the brittle nature and an increase in the flexibility of the pellets would be an advantage.

There are differences in the nature of the calcium polysaccharide gel, that forms on the surface of the coated pellets, and these have resulted in considerable differences in the morphology of the dry coatings and the mechanical properties of the coated pellets. It is reasonable to expect that these differences may also influence the hydration and release characteristics exhibited by these coated pellets. These issues will be discussed in a future publication.

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