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A novel gel formation method, microstructure and mechanical properties of calcium polysaccharide gel films

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Abstract

Hydrophilic gels, formed by the interaction of calcium ions with either sodium alginate or potassium pectinate, can be deposited as a wet coating on to the surface of drug loaded pellets. If the coated pellets are dried, they could be dispensed to a patient in a capsule for oral delivery of the active drug. In contact with the aqueous fluids of the gastrointestinal tract, the gel coat will rehydrate, swell and will sustain the release of active drug from the core. In order to facilitate the development and refinement of this novel coated system, it is beneficial to have a method that can produce free gel films in a manner that closely mimics the way the gel coat is formed and deposited on the pellet surface. Traditional film producing methods would involve the spraying or depositing (by evaporation) the gel forming polysaccharide on to an inert surface, drying it and then exposing the dry film to a solution containing calcium ions. Because the film is dry before it is gelled, it is fundamentally different to the wet gel coats that are deposited on to the pellets. We have developed a method to produce wet gel films and have evaluated different manufacturing conditions in order to optimize the quality of the completed gel film. Additionally, we have used these films to assess the effect that the type of polysaccharide and the environmental conditions experienced during rehydration (pH and ionic strength) has on the mechanical properties and the microscopic morphology of the gel. Irrespective of the rehydration medium, the calcium pectinate gel films were softer, weaker and more porous, than the calcium alginate films. Although calcium alginate gels that were rehydrated in 0.1 M NaCl were porous, the same films rehydrated in either water, simulated gastric fluid USP (without pepsin) or 0.1 M HCl were stronger and much more dense microscopically. Furthermore, of the four different alginates that were evaluated, those with a high content of guluronic acid saccharides were the strongest but most brittle when rehydrated in water.

Keywords: Film; Polysaccharide; Alginate; Pectin; Gel formation; Mechanical tests

1. Introduction

It is well known that the release characteristics of film-coated sustained release formulations are strongly dependent on the permeability and the mechanical properties of the film (Arwidsson, 1991). Aulton (1982) suggested that evaluation of free films as a means to predict the properties of applied films will be experimentally economical and statistically efficient. Variables such as the substrate to which the film is initially applied and the application technique must be considered. In general, a free film may be prepared by casting or by spraying the polymer solution on to an inert substrate to mimic a spray-coating process. The film is allowed to dry completely before being gently removed from the substrate.

Various physico-chemical and mechanical tests can be performed to characterize films, and these tests are generally performed on dry films in order to assess the performance of the coatings during further processing (e.g. compression of coated pellets) and storage. In addition, the homogeneity of a free film can be studied by scanning electron microscopy (Harris and Ghebre-Sellassie, 1997). However, the mechanical properties of the dry films are not good indicators of how the coated dose form will perform when in contact with aqueous fluids. Therefore, to more thoroughly understand the practical performance of the coated dose form, it is important to study the mechanical properties of the films in a wet or hydrated state, since these conditions mimic the *in vivo* conditions during drug release.

Anionic polysaccharides (e.g. sodium alginate and low methoxy potassium pectin) can react with calcium ions to form insoluble calcium gels. These gels can be applied by interfacial

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complexation on a core as a film coating for sustained release (Sriamornsak et al., 1997; Sriamornsak, 2002). Although calcium alginate films prepared by immersing dry cast alginate films in calcium solution have been studied (Julian et al., 1988; Aslani and Kennedy, 1996; Lim and Kennedy, 1997), these films may not be a good model for films deposited by interfacial complexation. In this study, a technique of calcium polysaccharide gel (CaPG) film formation, that mimics conditions pertaining to the interfacial complexation coating process, will be proposed. As well, microscopy and mechanical tests will be used to characterize these CaPG films in the dry and hydrated states.

2. Materials and methods

2.1. Materials

Low methoxy pectins with 28% esterification were obtained from two sources. A commercial pectin (LMA) with 20% amidation (GENUpectin type LM-104 AS-FS, CP Kelco, Denmark) was donated. A potassium salt of esterified (non-amidated) pectin from citrus fruit (LMC) and low and medium viscosity sodium alginates (ALV and AMV, respectively) obtained from *Macrocystis pyrifera* were purchased from Sigma Chemical Company (USA), and low viscosity sodium alginates obtained from *Laminaria hyperborae* leaves and stipes (i.e. LVM and LVG, respectively) were purchased from Pronova Biomedical (Norway). Flat-sheet dialysis membranes, Spectra/Por® Membrane (12,000–14,000 molecular weight cut-off) were purchased from Spectrum Laboratories, Inc. (USA). All other chemicals were of analytical reagent grade and were used as received. Deionized water prepared by reverse osmosis was used in all experiments.

2.1.1. Design and establishment of gel formation method and time

In order to prepare CaPG films that reflected the CaPG coating on pellets, a novel gel formation method was designed. The method allowed calcium ions to diffuse from a source to form gel films with pectin or alginate. Polysaccharide solutions (2% w/w) were prepared in deionized water. The solutions were stirred by magnetic stirrer for 2 h to ensure homogeneity and were then left undisturbed overnight to allow the air bubbles to rise. The polysaccharide solutions (30 g) were poured into the cylindrical mould (13 cm diameter, 5 cm deep in total and covered with dialysis membrane on one side) which was previously levelled (Niveau-level, E.D.A., France). The dialysis membrane was selected as a barrier to retain the polysaccharide but to allow calcium ions to diffuse through to form gels. One liter of 0.34 M calcium chloride was poured into the bath to start gelation at 25 °C. Diffusion of calcium through the membrane caused gelation of polysaccharides. See Fig. 1. The appearance of the gels and the time required to form stable gels was observed.

2.1.2. Establishment of post-gelation hardening time

CaPG gels were prepared by the above method using a gelation time of 60 min. Immediately after gelation, 40 mL of 0.34 M calcium chloride was added on to the top of the gel for 0, 15, 30 or 60 min. The mechanical properties of the hardened gels ($n = 3$) were measured as described below.

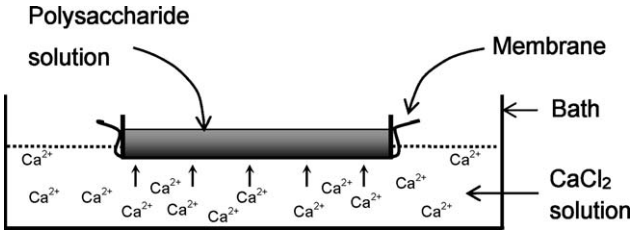

Fig. 1. Diagram of a novel design of calcium polysaccharide gel formation method.

2.1.3. Selection of washing time

CaPG films were prepared using 60 min gelation time and 30 min hardening time. Excess calcium was rinsed off with deionized water. The gels were then washed by soaking in deionized water with occasional shaking. The amount of calcium lost from CaPG films at different washing times (30, 60, 90, 120 and 180 min) was measured by using a complexometric titration technique. The washing water was changed every 30 min for the first 2 h.

Samples (5 mL) were manually taken from the known amount of water used for washing. One indicator buffer tablet (Merck, Germany) was added to the 5 mL sample and after it dissolved, 1 mL of ammonia solution (28% v/v) was added. The solution was titrated with 0.001 M sodium ethylenediamine tetraacetate (sodium EDTA) until the end point where the color changes sharply from apple red to emerald green. The determination was performed in triplicate. Standardization of sodium EDTA was conducted as follows. Approximately 50 mg (but accurately weighed) of chelometric grade calcium carbonate (dried at 105 °C for 2 h) was dissolved in 10 mL of 0.1 M HCl and then diluted to 100 mL with deionized water. After it dissolved, the solution was neutralized with 0.1 M NaOH. After that, the same procedure of titration as above was applied, and the molarlity of sodium EDTA was calculated based on three measurements. These data were corrected for blanks which were the same as above but did not contain calcium.

2.2. Determination of calcium diffusion through membrane

Calcium diffusion through the dialysis membrane used in this study was determined using side-by-side diffusion cells (custom made by LAB Supply, Australia). A hydrated dialysis membrane was placed between the two half cells of a diffusion cell and sealed with high vacuum grease. The temperature was the same as during the gel formation process, i.e. 25 °C. One hundred milliliters of water or 0.34 M $CaCl_2$ were filled into the receptor and donor cells, respectively. During the diffusion studies, continuous stirring was provided in the receptor cell with a magnetic stir bar driven at 300 rpm while the donor cell was static. At specific times, 1 mL of samples were manually collected and replaced with fresh medium. The calcium diffused was determined by titration as described above. The total membrane area available for diffusion was 12.57 cm^2.

2.3. Manufacture of CaPG films

CaPG films were manufactured by the same procedure as above using a gelation time of 60 min and hardening time of 30 min. The temperature was 25 °C in a static condition. Excess calcium was rinsed off with deionized water. The gel film was then washed by soaking in deionized water for 3 h, during which time the water was changed every 30 min for the first 2 h. After washing, the gel was left overnight in water at 25 °C. The gel was cut into pieces as required and these were dried in a hot air oven at 50 °C for 48 h. The dried pieces of gels were stored in a desiccator over silica gel until used.

2.4. Microscopic examination

A scanning electron microscope (Hitachi S2250-N, Japan) was used to examine the microstructure of the CaPG films. The films were air-dried in an incubator (50 °C) for 48 h. Rehydrated film samples were obtained by immersion of the dried gel films in deionized water, 0.1 M HCl, simulated gastric fluid USP without pepsin (SGF) or 0.1 M NaCl for 24 h, followed by freeze-drying (Christ Alpha 1-4 model, B. Braun Biotech International, Germany). All samples were broken for cross-section observation and then mounted on SEM stubs using double-sided carbonized adhesive tape. The accelerating voltage was 10 kV.

2.5. Measurement of mechanical properties

The mechanical strength of the wet, dry and rehydrated (24 h immersion in either water, 0.1 M HCl, SGF or 0.1 M NaCl) CaPG films was performed with a Lloyd universal tensile tester (model Mk2, Lloyd Instruments, UK), instrumented with a 500 N load cell. The device consisted of a puncture probe and a film holder that was adapted from those previously described (Radebaugh et al., 1988; Bodmeier and Paeratakul, 1993). The wet and rehydrated films were carefully blotted to remove water from the film surface. The thickness of wet, dry and rehydrated films was determined in five positions using a micrometer (model 7309, Mitutoyo Corporation, Japan). The film specimens (45 mm in diameter) were positioned in the film holder between two mounting plates. The puncture probe (96 mm in length and with a 5 mm diameter hemispherical tip) was attached to the crosshead, which was then driven downward through the center of the mounted film at a speed of 5 mm/min. The diameter of the opening in the film holder was 19 mm. Data evaluation was performed by Nexygen 2.0 software (Lloyd Instruments, UK) which was also used for operating the instrument. The instrument was installed in a controlled-temperature room, which was held at 25 °C. The films were strained until load failure occurred. The load (N) and displacement (m) at break were converted to puncture strength (MPa) and % elongation. Puncture strength was calculated by Eq. (1):

$$\text{puncture strength} = \frac{F}{A_{cs}} \quad (1)$$

F is the load at puncture (N) and A_{cs} is the cross-sectional area of the edge of the film located in the path of cylindrical hole of the film holder (m^2). Division by A_{cs} normalizes the data for differences in thickness from film to film (Radebaugh et al., 1988). Puncture strength is a measure of toughness and is directly proportional to resistance to break or fracture film (Radebaugh et al., 1988).

The elongation to puncture was calculated by Eq. (2):

$$\text{elongation to puncture} = \frac{\sqrt{(R^2 + D^2} - R}{R} \times 100 \quad (2)$$

where R is the radius of the film exposed in the film holder (m) and D is the displacement of the probe from the point of contact to the point of film puncture (m).

2.6. 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 were 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. Rationale for establishment of gel forming conditions

The evaluation of free films has been established as a valuable tool in the development of film coating systems, since it can be readily used to characterize and evaluate fundamental properties of the coating. Although calcium alginate films prepared by immersing dried cast alginate sheets in calcium acetate solution have been studied (Julian et al., 1988; Aslani and Kennedy, 1996; Lim and Kennedy, 1997) the gels are fundamentally different to the coatings produced by interfacial complexation. Cast films are dried prior to gelation, whereas films produced by interfacial complexation are gelled prior to drying.

A novel gel formation method was developed to prepare CaPG films that mimic the interfacial complexation CaPG coating on pellets. A unique property of the new method is that calcium ions diffuse unidirectionally from a source containing 0.34 M calcium ions through a membrane to form a cross-linked polysaccharide gel film on the membrane. The cross-linking reaction was originally described by Grant et al. (1973) in terms of an 'egg-box model' for the cooperative mechanism of binding involving two or more chains. In the case of pectin and alginate, they proposed that gel formation was the result from a specific interaction between calcium ions and blocks of galacturonate and guluronate residues, respectively. However, more recent studies strongly suggest that mannuronate–guluronate blocks are also involved in calcium ion gelation of alginate (Braccini and Perez, 2001; Donati et al., 2005).

Over the past 30–40 years a vast literature on the use of the alginate and pectin gels for purpose of entrapment of drugs, proteins and cells has developed. In a large number of those publications, 5% w/v calcium chloride dihydrate (i.e. 0.34 M calcium ions) was chosen as the gelling agent. We also chose

that concentration, since a previous study from our group (Aslani and Kennedy, 1996) clearly demonstrated that similar (but intrinsically more robust) films produced at lower calcium concentrations were fragile and very difficult to work with. The calcium flux, calculated from the slope of the plot of the amount of calcium diffused through dialysis membrane per area versus time, was 0.00529 μg/cm^2/s. However, during gel formation, the calcium may diffuse more slowly due to the viscosity of the polysaccharide as well as the barrier property of the forming CaPG gels.

The conditions for establishment of gel formation by calcium diffusion through dialysis membrane were studied. The results showed that the shortest gelation time for the complete formation of the stable gel (no liquid left and removable) varied among polysaccharides, i.e. 30 min (for LMC and LMA), 45 min (for ALV, LVM and LVG) and 60 min (for AMV). In order to set a standard preparation procedure, a 60 min gelation time was chosen.

The hardening time (i.e. the time the gel was soaked in 0.34 M calcium chloride after gelation), that was required to get a gel with maximum strength, was determined by mechanical tests on the wet gel films. The effect of hardening time on the puncture strength and elongation of CaPG films is shown in Fig. 2. This shows that at least 15 min is required for LMC, ALV and AMV, while 30 min is required for LMA and LVM to reach the maximum mechanical strength. There was no significant difference among the hardening times used for LVG. Therefore, a 30 min hardening time was chosen as a standard gel forming condition.

Excess calcium salt left in the gel films would interfere with the measurement of cross-linked calcium and may also alter the mechanical properties of the film. Therefore, the washing step removes unbound excess calcium ions in the gel films. In the establishment of standard gel forming conditions, the hardened gels were washed for different times and the amount of calcium released in the washing water was determined by chelometric titration. Fig. 3 shows the cumulative calcium lost during the washing process. Most calcium loss occurred in the first hour, and negligible calcium was lost after washing for 180 min. Hence, a 180 min washing time, with water changed every 30 min for the first 2 h, was used in the manufacturing of calcium gel films.

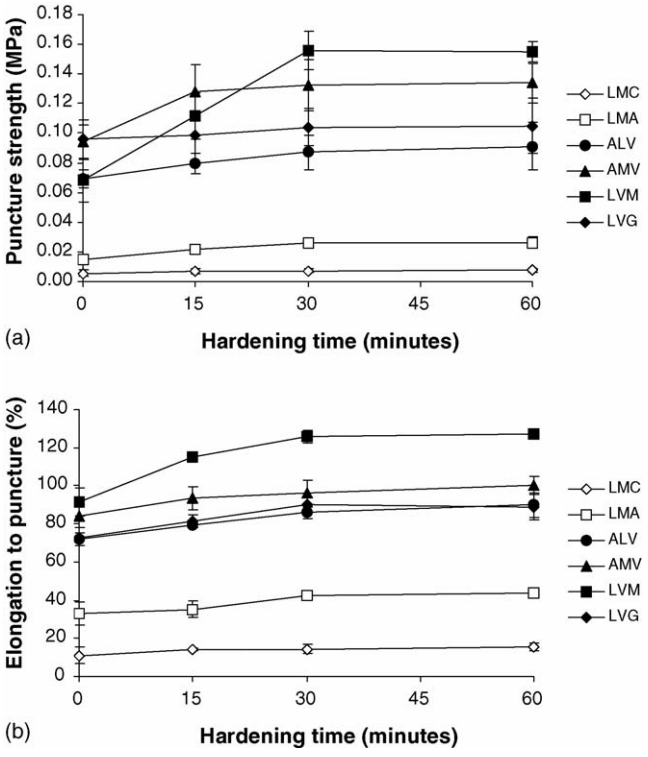

Fig. 2. Effect of hardening time on (a) puncture strength and (b) elongation to puncture of calcium polysaccharide gel films ($n = 3$).

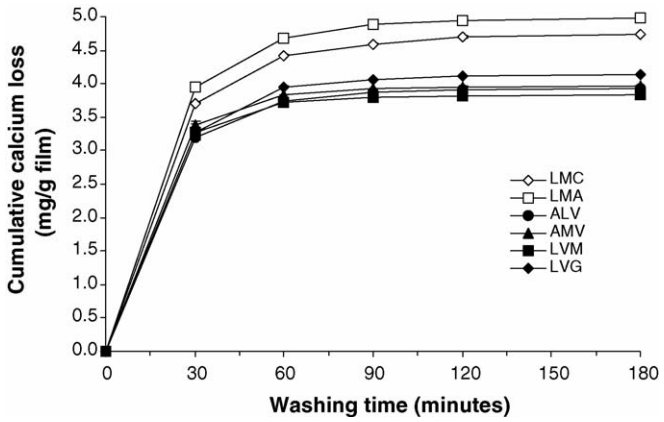

Fig. 3. Cumulative calcium loss from calcium polysaccharide gel films during washing steps. The means of triplicate data are plotted; the standard deviations are within the point size.

3.2. Morphology of CaPG films

Figs. 4 and 5 show scanning electron micrographs of the structure of dry LMA and ALV films and the films after exposure to different media for 24 h. Scanning electron micrographs of other calcium gels displayed similar characteristics. The internal structure of dry films (Figs. 4a and 5a) was dense but with some cracks. Calcium pectinate gel films exposed to acidic media and water extensively swelled (perhaps due to calcium loss allowing water uptake) and showed a porous sheet-like structure. For alginate, however, the microstructure of calcium films exposed to acidic media and water was fairly similar and dense. This suggests that the changes in molecular structure or calcium content did not substantially influence the microscopic structure of these films.

In 0.1 M NaCl, after extensive swelling, both the LMA and ALV showed a loose and porous structure. No substantial difference in the appearance was observed among calcium films with different types of polysaccharide. Partial transformation of calcium polysaccharides to soluble sodium polysaccharides may allow more water to be absorbed and consequently promote a porous structure.

The differences in the nature of the CaPG films as well as the ion-exchange behavior of these films after exposure to different media have resulted in considerable differences in the morphology of the exposed films. It is reasonable to suggest that these differences may influence the mechanical properties as well as permeability of these CaPG gel films.

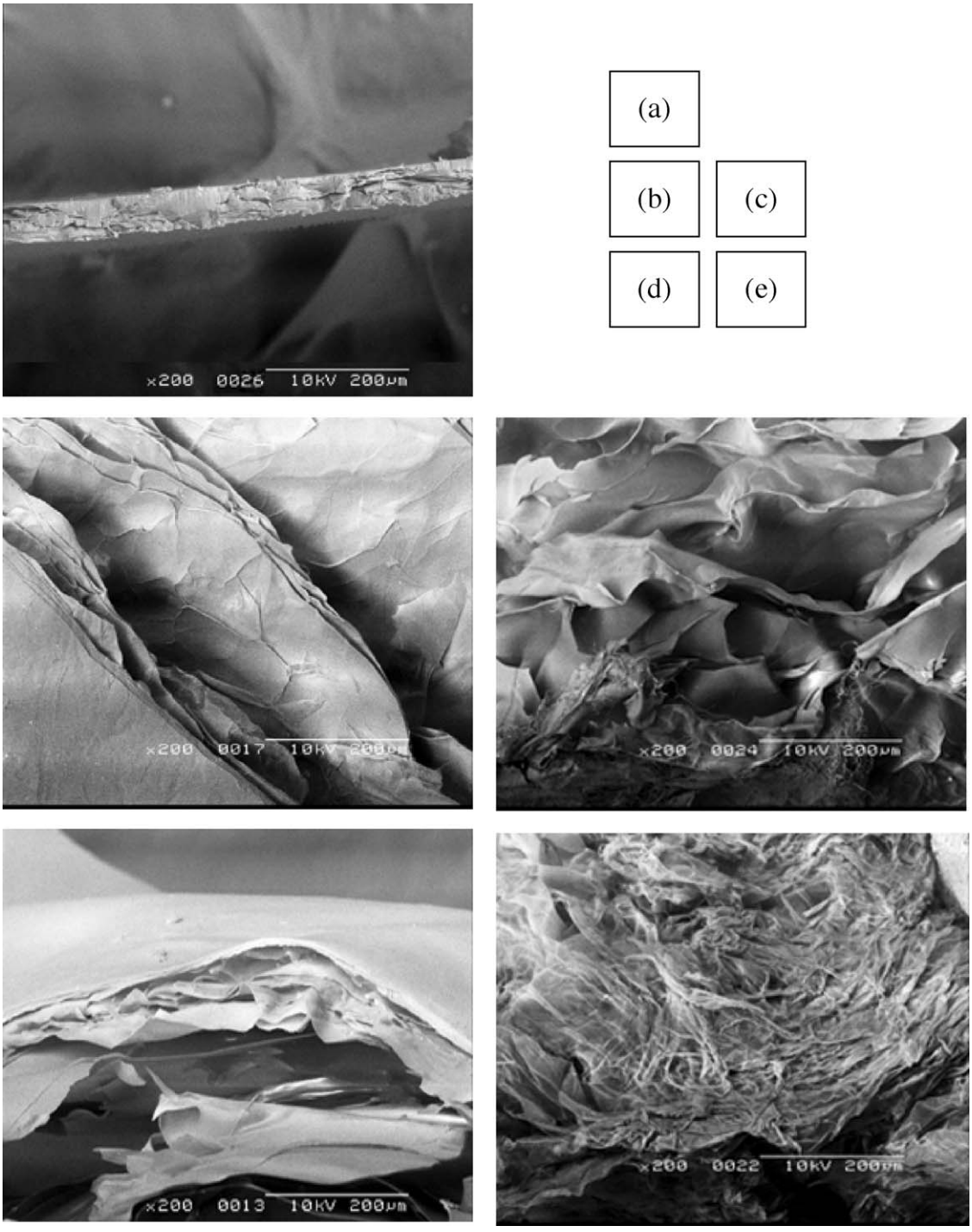

Fig. 4. Scanning electron micrographs of the cross-section of calcium pectinate (LMA) gel films; (a) dry film and film exposed to (b) 0.1 M HCl, (c) SGF, (d) water and (e) 0.1 M NaCl for 24 h. Magnifications and scale bars are shown on the individual photographs.

3.3. Mechanical properties of CaPG films

The mechanical properties of coating films are important characteristics, since they may help predict the stability and release behavior of film-coated dose forms and also provide information concerning possible interactions between components (e.g. plasticizers) in the coating films. In particular, the elastic modulus and the tensile strength are considered good indicators of coating performance (O'Donnell and McGinity, 1997). A high tensile strength may promote abrasion resistance but taken to a more extreme value may be indicative of a brittle material and this may increase the incidence of coat defects and cracking. Clearly, these could severely compromise the release profile of the product. Brittleness and stiffness may also be related to a high elastic modulus and a low elongation to puncture. A high puncture strength and elongation to puncture may be

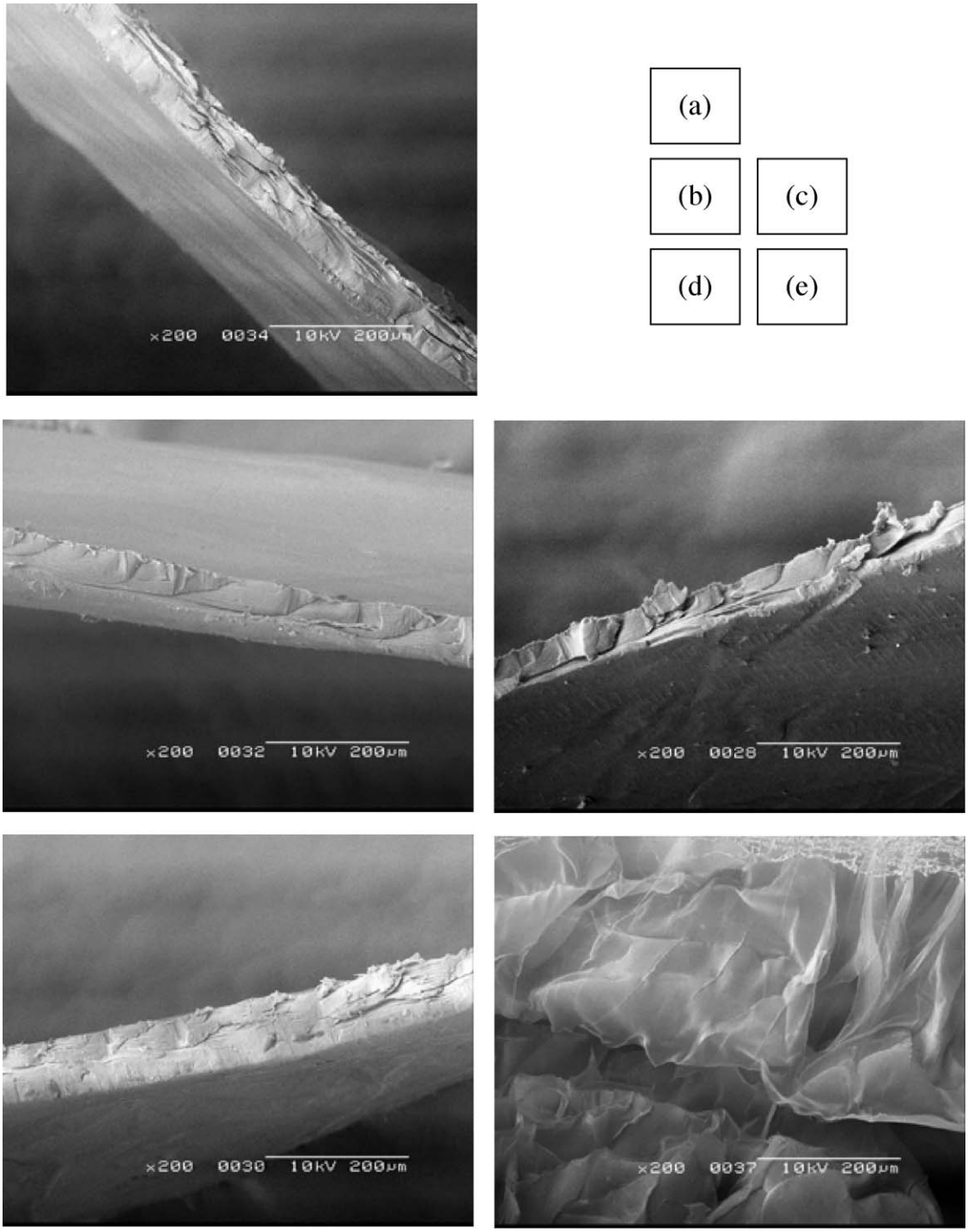

Fig. 5. Scanning electron micrographs of the cross-section of calcium alginate (ALV) gel films; (a) dry film and film exposed to (b) 0.1 M HCl, (c) SGF, (d) water and (e) 0.1 M NaCl for 24 h. Magnifications and scale bars are shown on the individual photographs.

associated with film toughness and resilience (Radebaugh et al., 1988). These are both desirable qualities in a coating film since they mitigate against mechanical failure of the coating film. The mechanical properties of rehydrated films, for example during release studies or under *in vivo* conditions, may be completely different from those in the dry state. Therefore, it is of great interest to know how the rehydration medium affects the mechanical properties of the films. In this study, the load and displacement at rupture, of wet, dried and rehydrated CaPG films were measured by a puncture test. The load was measured as a function of probe displacement, and the load and displacement at puncture were converted to puncture strength and percentage elongation to puncture.

Fig. 6 shows the mechanical properties of wet, dried and rehydrated (in water) CaPG films. The wet films had the lowest puncture strength and highest elongation to puncture for all

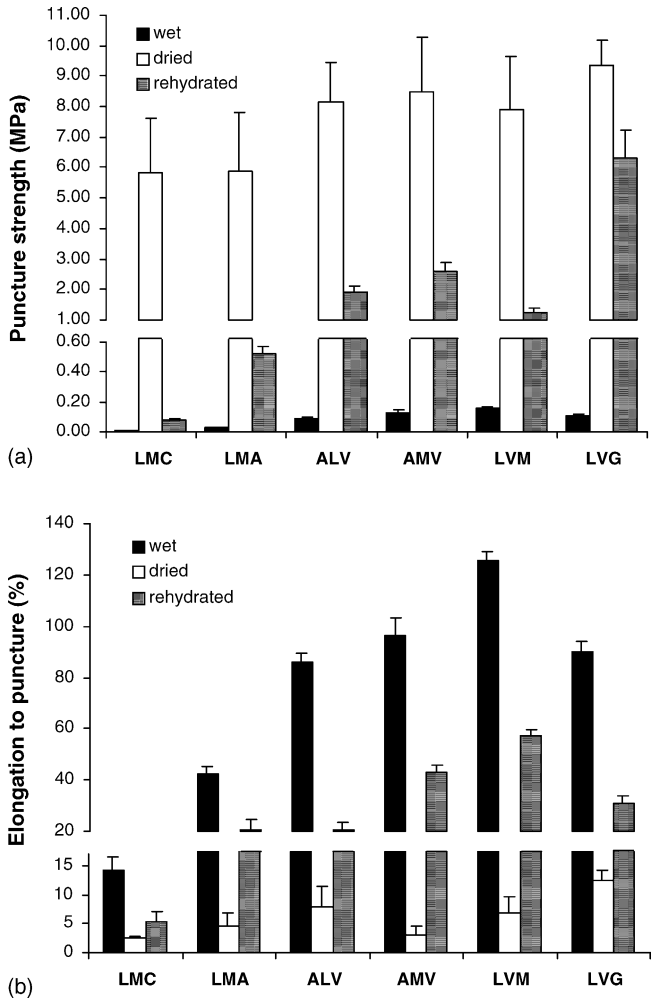

Fig. 6. (a) Puncture strength and (b) elongation to puncture of wet, dried and rehydrated (in water) calcium polysaccharide gel films ($n = 3$).

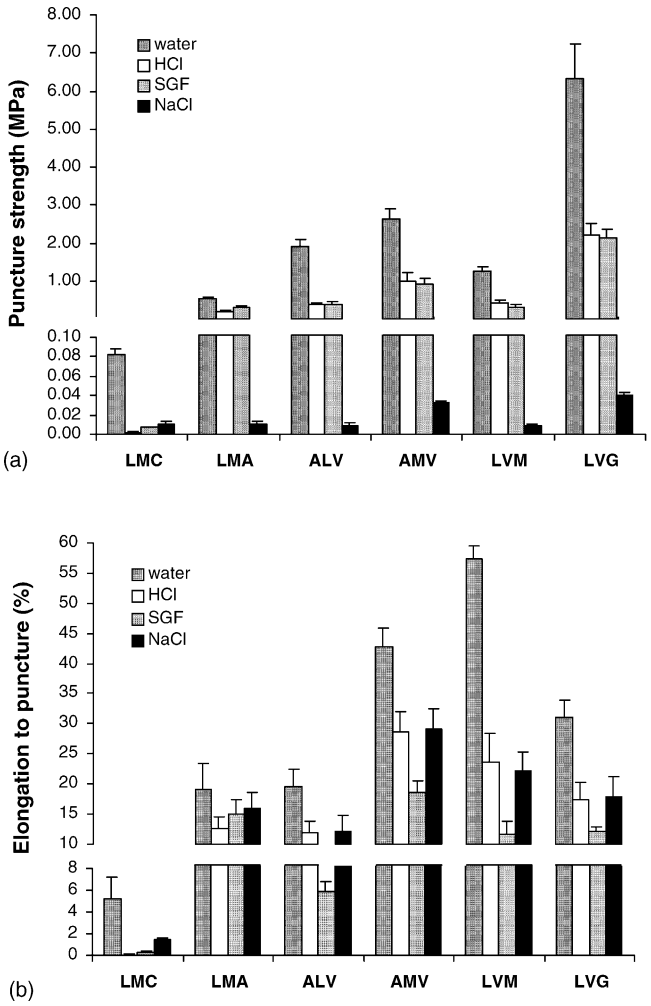

Fig. 7. Effect of medium on (a) puncture strength and (b) elongation to puncture of calcium polysaccharide gel films ($n = 3$).

polysaccharides tested. The wet films were soft and flexible. Water generally causes a decrease in the intermolecular forces resulting in a decrease in the glass transition temperature (Joshi and Wilson, 1993), mechanical strength and the brittleness of polymeric materials (Bodmeier and Paeratakul, 1993). The wet calcium pectinate films were softer and weaker than calcium alginate. LMA was slightly stronger than LMC, even though the calcium content in LMA was less. This is probably due to the amide groups in LMA, which allowed chain association through hydrogen bonding (Racape et al., 1989). The wet films of all calcium alginates showed comparable mechanical properties to each other.

Fig. 6 also shows that dried CaPG films were hard and brittle; they had high puncture strength and low elongation to puncture. Dry films were either broken into many small pieces or were star-cracked upon puncture. There was no statistically significant difference among the dried calcium films made of different polysaccharides. The films rehydrated in water for 24 h (i.e. rehydrated films), were not as brittle as the dry films, had a circular puncture hole in the middle of the film specimen and a non-recoverable hat-shape after the test. As shown in Fig. 6, rehydrated films had lower puncture strength and higher elongation to puncture than dried films. The significant increase (2–13-fold) in percentage elongation could be due to water plasticizing the films.

The puncture strength of the wet and rehydrated films was significantly different in that rehydrated films had higher puncture strength than the wet films, which indicated that the rehydrated films were stronger. Although the wet films of CaPG were quite flexible, the corresponding rehydrated films were less flexible (lower values of percentage elongation in Fig. 6). This suggests that the drying process altered the ability of the film to rehydrate. Drying results in the removal of most of the water molecules associated with the gelled network. The gel network probably loses its ordered arrangement and partially collapses. Although this change in the gelled network can be restored on rehydration, it is apparently not fully restored, as the films do not regain their original characteristics.

Fig. 7 shows the mechanical properties of CaPG films after rehydration in different media. Comparison of the CaPG films exposed to water (rehydrated films), 0.1 M HCl, SGF and 0.1 M NaCl indicated that films exposed to water gave the highest puncture strength and elongation in most cases. In all other media, the mechanical properties were reduced due to changes in the

calcium film properties. It has been suggested that, in acidic media, the calcium films were converted to acid films (Aslani and Kennedy, 1996; Lim and Kennedy, 1997; Sriamornsak, 2002). This transformation would influence the mechanical properties of the CaPG films exposed to 0.1 M HCl or SGF. The puncture strength and elongation of films exposed to acidic media were significantly decreased, compared to calcium films exposed to water. Scanning electron microscopy examination revealed that calcium pectinate gel films exposed to acidic media had a loose structure while those exposed to water had a dense structure (see Fig. 4). This may cause a low puncture strength and elongation of calcium pectinate gel films exposed to acidic media. However, for alginate, the microscopic structure of calcium films exposed to acidic media was not visibly different from those exposed to water (see Fig. 5) even though their mechanical properties were reduced. In addition, there was no significant difference between the puncture strength of calcium films exposed to 0.1 M HCl or SGF, in all polysaccharides tested. However, the elongation to puncture of all calcium alginate films exposed to 0.1 M HCl and SGF were significantly different.

The calcium films exposed to 0.1 M NaCl were very soft as shown by very low puncture strength (Fig. 7a). These results could be explained by the displacement of calcium ions from the CaPG gel films (Sriamornsak, 2002). Scanning electron micrographs of calcium films exposed to 0.1 M NaCl revealed a very porous structure, which could also account for the low puncture strength of the films exposed to 0.1 M NaCl. Likewise, after exposure to 0.1 M NaCl, the films (except LMA) were significantly weaker or less flexible than the films exposed to water as shown by a lower percentage elongation (Fig. 7b).

In general, from Fig. 7, the calcium films made of pectins were softer and weaker, compared to calcium alginate films, after exposure to all media. This might be explained by the substitution of free carboxy groups by methoxylation and/or amidation, which decreased the chance for calcium cross-linking. Calcium films of LMA were stronger and more flexible than those of LMC. Hoefler (1991) suggested that the calcium gels of LMC were soft whereas LMA gave a rubbery gel. This may be due to the strong association through hydrogen bonding between amide groups in LMA (Racape et al., 1989). Calcium films of high M alginates (i.e. ALV, AMV and LVM) had similar strength after exposure to each media. However, the films of LVG (with high G content) gave highest puncture strength in all media, probably due to the greater calcium binding and consequently cross-linking.

4. Conclusions

A novel gel formation method was developed in order to prepare free films that mimic the CaPG coating on pellets. Scanning electron microscopy examination of the microstructure revealed that, in contrast to rehydrated films, dried films had a dense structure. Calcium pectinate gel films showed a porous structure after rehydrating in all media. Rehydrated calcium alginate gel films were dense except when rehydrated in 0.1 M NaCl. Wet CaPG films were soft and flexible while the dried films were hard and brittle. Films rehydrated in water were intermediate between dried and wet films and this suggested that the drying process altered the ability of the films to rehydrate. Films rehydrated in other media (i.e. 0.1 M HCl, SGF and 0.1 M NaCl) were softer and weaker than when rehydrated in water; the 0.1 M NaCl had the greatest impact. The changes in mechanical properties of these rehydrated films may relate to the calcium content in the films after rehydration as well as the increased porosity of the rehydrated films. We are continuing our experiments with these systems, in particular to investigate their swelling and diffusion properties.

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