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Study of the effect of lactose on the structure of sodium alginate films

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ABSTRACT

The aim of this study was to evaluate the interaction between the film-forming sodium alginate and lactose monohydrate. This combination is used in the co-spray-drying technique for microencapsulation, but no respect on the structure of the film formed has not been published previously. From mechanical tests, positronium lifetime measurements and FT-IR studies on free films containing different ratios of film-former and lactose, we concluded that the mechanical strength of the sodium alginate film decreased with the increasing proportion of lactose. The free volume in the polymer matrix decreased to a minimum as the lactose content was progressively increased to 40%, but subsequently increased at higher lactose contents. The explanation of this phenomenon is the filling of the holes with the sugar. As lactose became predominant component, the structure of the polymer network weakened. These conclusions were supported by the FT-IR findings. The present results permit a clear explanation of the previously reported favourable effects of this film-forming combination on the dissolution of the active agent from the microcapsules.

1. Introduction

Film coating is a technological step that is widely used in the formulation of solid dosage forms (Bauer, Lehmann, Osterwald, & Rothang, 1988; Cole, Hogan, & Aulton, 1995). It is applied not only to coat a final dosage form but also for the surface treatment of intermediate products. The processes for the coating of pellets and granules are well established (Larsen, Sonnergaard, Bertelsen, & Holm, 2003; Siepmann, Siepmann, Walther, MacRae, & Bodmeier, 2006), but nowadays the aspects of the surface treatment of micronized components should also be considered (Jono, Ichikawa, & Miyamoto, 2000). In this case, the methods and parameters are different from those applied for conventional coatings (mainly involving fluid bed procedures). The fluid bed technique with a Wurster column is a popular method for large particles, but the formulation of irregularities and the extensive aggregation of small particles are inevitable (Heng, Chan, & Tang, 2006; Tang, Wang, Liew, Chan, & Heng, 2008). Thus, some modification of the original treatment or the introduction of new surface-treatment methods is unavoidable inescapable. The co-spray-drying technique of a dispersion containing film-forming materials (polymers and additives) and insoluble active agents can be applied to prepare a surface-coated product (microcapsules) (Al-Zoubi, AlKhatib, Bustanji, Aiedeh, & Malamataris, 2008; Brandau, 2002).

The solubility, digestibility and mechanical behaviour of the films formed must be appropriate for the planned application of the films (Fulzele, Satturwar, & Dorle, 2002; Lafferty, Newton, & Podczeck, 2002; Leong et al., 2002). Microcapsules are utilezed mainly for the formulation of modified release preparations (Biju, Saisivam, Maria Gerald Rajan, & Mishra, 2004; Liu, Ichikawam, Cui, & Fukumori, 2006; Lu, Wen, Yang, & He, 2007). In this case, polymers with special solubility properties (enteric soluble and permeable) must be used. Microparticles can be applied to increase the dissolution of poorly-soluble active agents (Ozeki et al., 2005; Wong, Kellaway, & Murdan, 2006) and also for targeting (Devy, Balasse, Kaplan, Madoulet, & Andry, 2006; Zhang, Wu, Liu, Chen, & Lin, 2008) and taste masking (Xu, Bovet, & Zhao, 2008).

Polymers that form water-soluble films are popular for the surface treatment of pellets and tablets (Guo, Skinner, Harcum, & Barnum, 1998). Alone or in combination with other ingredients (e.g. light-protective pigments), they protect the active agents from other components, light, moisture and oxygen (Cole et al., 1995). They can increase the processibility of crystals (Bajdik et al., 2002, 2004). This field of spray-drying microencapsulation is not well known in spite of its possible favourable effects. We aim to include this technique in improved methods for the processing of materials.

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The film formers and additives applied in the spray-drying technique and the requirements that they must satisfy are the same as or similar to those of the coating materials used in other procedures (there are some exceptions, e.g. colourants are not typically used for the formulation of microcapsules).

The alginates, well-studied, water-soluble, linear polysaccharides that are extracted from brown seaweed (Rioux, Turgeon, & Beaulieu, 2007). Alginate contains two uronic acids, α-l-guluronic and β-d-mannuronic acids, and is composed of homopolymeric blocks and blocks with alternating sequences (Pongjanyakul, 2009). Generally, insoluble gel formation has been demonstrated to result from specific interactions between divalent ions and blocks of α-l-guluronic residues. Swelling, gel and film-forming properties of alginates are well known (Murata, Sasaki, Miyamoto, & Kawashima, 2000; Sriamornsak & Kennedy, 2008). They are often applied in pharmaceutical technology to produce different dosage forms (Babu, Sairam, Hosamani, & Aminabhavi, 2007; Chan, Lee, & Heng, 2006; Kubo, Miyazaki, & Attwood, 2003; Sriamornsak, Thirawong, & Korkerd, 2007).

The use of lactose in co-spray-dried products prepared with alginate was suggested earlier (Takeuchi, Nagira, Yamamoto, & Kawashima, 2005), our previous results revealed that this combination not only enhances the dissolution of the active agent, but also changes the surface free energy of the intermediate product and consequently its handling (Makai, Bajdik, Erős, & Pintye-Hódi, 2008). The effects of different additives on the structures of films are currently undergoing extensive study (Bajdik et al., 2005; Pintye-Hódi et al., 2006; Pongjanyakul & Puttipipatkhachorn, 2008; Tarvainen et al., 2003), but the manner in which lactose exerts its effects on the properties of alginate films has not yet been fully elucidated. Although the application of this sugar in a water-soluble film is not typical, it is known at least that the lactose in the dried film is amorphous (Bajdik et al., 2008). To gain a clearer picture, free films were prepared from different ratios of lactose and sodium alginate in this study and their properties were examined by means of mechanical tests, Infrared ATR experiments and positronium lifetime measurements. Such results can reveal the relationship between components and promote an understanding the film-forming process on the surface of crystals and the structure of the films formed.

2. Experimental

2.1. Materials

Sodium alginate (Manugel GHB, ISP Co, UK), and α-lactose monohydrate (Ph.Eur.) (Sigma, Hungary) were used in the experiments.

2.2. Preparation of free films

Aqueous 2% solutions were prepared in which the sodium alginate:lactose ratio was 100:0 (Sample 1), 80:20 (Sample 2), 60:40 (Sample 3) 40:60 (Sample 4) or 20:80 (Sample 5). Three grams of each liquid was poured onto an even circular teflon surface with a diameter of 3.3 cm, and allowed to dry under ambient conditions (25 ± 2 °C and 50 ± 5% RH). The dried samples (after 24 h drying) were stored for 24 h in a desiccator (<20% RH/room temperature) and were examined with the two solvents. The moisture content of the films therefore was lower than 3%.

2.3. Determination of mechanical properties of films

A coating film must be sufficiently elastic for damage not to occur in it during subsequent technological processes. Thus, the strengths of such films must be tested. The strength tester and the software used were developed in our institute (Bajdik, Fehér, & Pintye-Hódi, 2007). This device contains a special specimen holder (20 mm in diameter) and a hemispherical stamp with a surface of 201 mm^2, and is connected to a computer via an interface. Thus, the ultimate deformation force can be measured, and the deformation process (force-time and force-displacement curves) can be followed. The round specimen is situated horizontally and the stamp moves vertically.

The measuring range was 0–200 N, the speed of the stamp was 20 mm/min, the sampling rate was 50 Hz, the output was 0–5 V, and the sensitivity was ±0.1 digit. The sensor was UNICELL force measuring equipment, calibrated with the C9B 20 kN cell. 10 parallel measurements were performed on each specimen.

Before the strength-testing experiments, the film thickness was measured with a screw micrometer with an accuracy of 0.001 mm (Mitutoyo, Japan).

2.4. Positronium lifetime measurements

Free volumes were measured via the determination of the lifetime of ortho-positronium atoms in the films. Positron lifetime spectroscopy is a method often applied to polymers that are used in pharmaceutical technology (Hiemenz, 1984; Kilburn et al., 2002; Süvegh et al., 1999). This procedure makes use of the phenomenon that, if positrons are injected into a polymer, a large number of them form atom-like bound-states with electrons. The lifetime of these “atoms” (the positronium) depends on the size of the free volume holes. The exact dependence can be approximated by a simple model, assuming spherical voids (Eldrup, Lightbody, & Sherwood, 1981),

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1}$$

where τ is the lifetime of the ortho-positronium atoms in nanoseconds, R is the radius of voids in Ångströms, and ΔR is a constant. For a molecular scale, the provided radii give a good fit to the BET and neutron scattering results.

The lifetime spectrometer applied was constructed from BaF$_2$-based detectors and standard ORTEC electronics. Spectra were collected in the 4096 channels of a multichannel analyzer. The time/channel value was ~10 ps and the time resolution of the system was ~210 ps. As positron source, carrier-free ^{22}NaCl was used sealed between kapton foils. The activity of the source vas $\sim 5 \times 10^5$ Bq and only 5–8% of the positrons were annihilated in the source itself.

2.5. FT-IR experiments

The free films were monitored with an FT-IR (AVATAR 330 FT-IR, Thermo Nicolet Corp., Madison, USA) apparatus, with an HATR accessory. Multi-bounce HATR with a standard zinc selenide crystal involved the following features: angle of incidence 45°, and depth of penetration 2 μm at 1000 cm^{-1}.

3. Results

3.1. Mechanical properties

The mechanical testing results revealed that the characteristics of the deformation curve (force-time) did not change appreciably with variation of the composition of the film. The films were mostly elastic, their curves containing two linearly increasing sections with different slopes (the deformation process started with a short elastic part) (Figs. 1 and 2). The deformation points were sharp and there was no obvious viscoelastic section. Decreasing

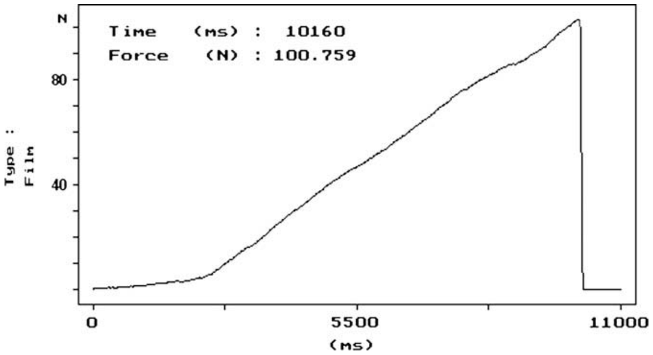

Fig. 1. Deformation curve of Sample 1.

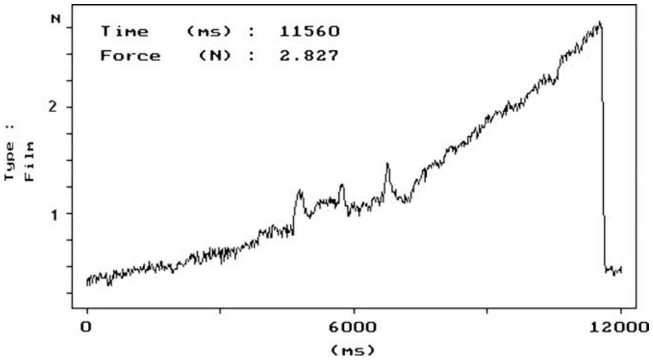

Fig. 2. Deformation curve of Sample 4.

polymer content was accompanied by significant ($p < 0.05$) reduction in the breaking force (Table 1). The film formed from the Sample 5 liquid was inadequate for this test and the film formed broke during drying ("spider web"-like). The development of the small pieces of this film (width was about 1–2 mm) was detected. These segments partly detached from the surface. The thickness of the pure polymer film was the highest. There was no obvious connection between the thickness of a sample and its mechanical properties.

3.2. Positronium lifetime measurement

Important pharmaceutical phenomena in polymers used to formulate solid dosage forms can often be explained by determining the size of the free volume holes in the polymer (Süvegh & Zelkó, 2002). For the alginate/lactose system, the most prominent feature is that the ortho-positronium lifetime is quite short, varying between 1200 and 1400 ps. Although this indicates very small free volume holes (Table 2), such a short lifetime is normal for sugars. The low positronium formation intensity (7–8%) is also characteristic of sugars or cellulose derivatives.

It is interesting that the lifetime-concentration curve is not monotonous. If the film were merely a simple physical mixture of the components, the lifetime would change monotonously with the concentration. However, the lifetime curve exhibited a minimum at $\sim$40% lactose, indicating a minimum size of the free volume at this composition.

Table 1
Parameters of free films.

	Lactose content (%)	Film thickness (μm)	Breaking force (N)
Sample 1	0	72 ± 7	97.67 ± 5.91
Sample 2	20	62 ± 8	56.28 ± 5.24
Sample 3	40	58 ± 4	29.61 ± 5.61
Sample 4	60	61 ± 6	3.64 ± 1.39

Table 2
The ortho-positronium lifetime in alginate/lactose films and the average size of free volumes.

	Lactose content (%)	ortho-Positronium lifetime (ps)	Free volume (Å^3)
Sample 1	0	1376 ± 16	2.51
Sample 2	20	1289 ± 26	2.15
Sample 3	40	1198 ± 8	1.84
Sample 4	60	1227 ± 12	1.93
Sample 5	80	1361 ± 10	2.45

The existence of a minimum in Table 2 is well outside the experimental error. This indicates that the alginate and lactose molecules interact with each other to form a more-or-less ordered structure. Nevertheless, the interaction can not involve strong secondary bonding, since it does not affect the mechanical properties of the films. Some weak orientational force during film formation might be the best candidate to explain the minimum, but a nanoscale phase separation at that concentration cannot be excluded. Either way, the result is that, at low lactose ratios, the small lactose molecules are incorporated into the spaces between the alginate chains. These spaces are not large enough for the whole lactose molecule to fit into them. However, the film-forming method may well allowed the existence of a structure in which lactose molecules alternate with alginate chains. This new structure furnishes a smaller free volume, but a mechanically weaker film up to the lactose concentration at which the minimum is observed.

Above that concentration, the increasing number of lactose molecules destroy the original alginate structure completely by separating the chains. This weakens the film further, but as it can be expected, increases the free volume. At the highest lactose concentrations, one does not expect a "real" film but almost independent alginate chains separated by large lactose inclosures. These lactose nanophases are not very large because they were not observed otherwise than through physically weakening the films. For such a system, theory predicts a complex o-Ps lifetime because an increasing number of positronium atoms form and annihilate in lactose nanophases. Consequently, at the highest lactose concentration, the observed lifetime must be very close to that measured in pure lactose. However, positron lifetime measurements cannot decide on nanoscale phase separation alone.

To decide on the nature of the observed interaction between alginate and lactose molecules, we performed an FT-IR study on the films.

3.3. FT-IR experiments

The measured spectra of the sodium alginate–lactose films with various compositions are depicted in Fig. 3. It is obvious that the spectra are dominated by the sodium alginate component and that the relative intensities of some bands are modified by the addition of lactose. First of all, although sodium alginate was used to prepare the film, the strong peak at $\sim$1725 cm^{-1} (peak (a), assigned to the νC=O stretching mode) indicates that the bulk of the polymeric acid is in protonated form. The broad band at $\sim$1645 cm^{-1} (peak (b)) is that of to the OH in-plane deformation mode of water present in the film, and the OH groups of both components. Its intensity increases on the addition of lactose. The other region influenced by increasing amount of lactose, is between 1200 and 1000 cm^{-1}, where the stretching modes of the combinations of the C—O and ring C—C bonds are to be found. Despite, these spectral regions of both components being well-structured, the films

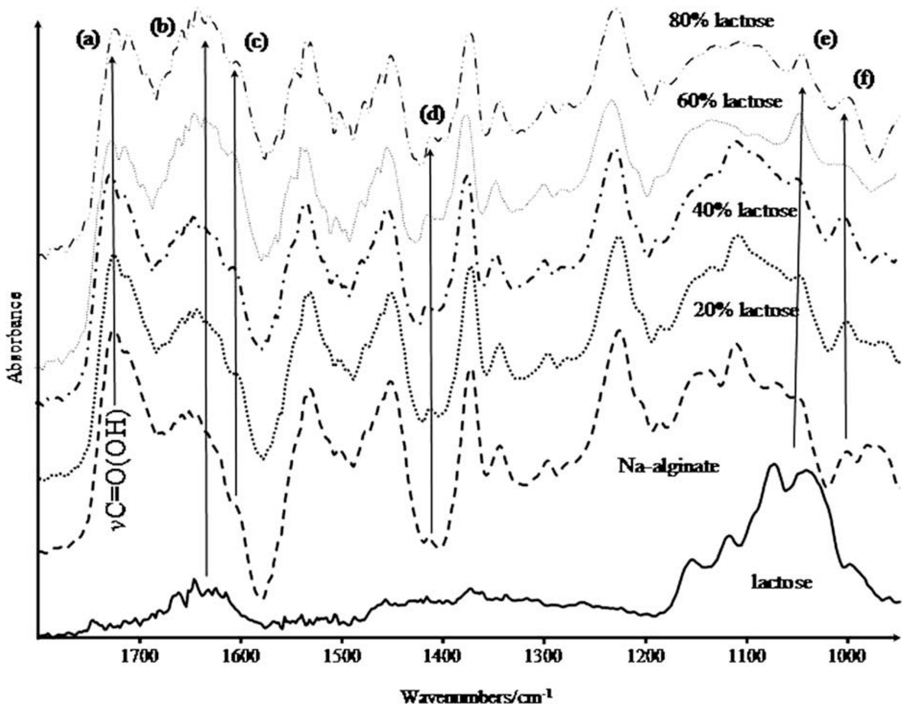

Fig. 3. Infrared ATR spectra of the alginate–lactose films with various composition and the pure components. Peak (a) indicates the presence of carboxylic groups, while (b) is assigned to the in-plane OH bending of both components and the water present in the system. Peaks (c) and (d) are new bands with increasing intensity, and peaks (e) and (f) are enhanced by the addition of lactose.

give a broad, non-structured band on the addition of lactose. Only peaks (e) and (f) are enhanced by increasing lactose content, but they are present in both components, due to the presence of the pyran rings in both components.

A pair of weak new bands can also be identified, at ~1586 and 1405 cm^{-1} (peaks (c) and (d)). These bands can clearly be identified by subtracting the spectrum of the pure sodium alginate film from the others. These difference spectra are given in Fig. 4. The positions and the shapes of these two broad bands are characteristic of the carboxylate (COO$^-$) groups (Socrates, 2005). Since the intensities of these bands increase with increasing lactose content, it may be supposed that the interaction between the polymeric

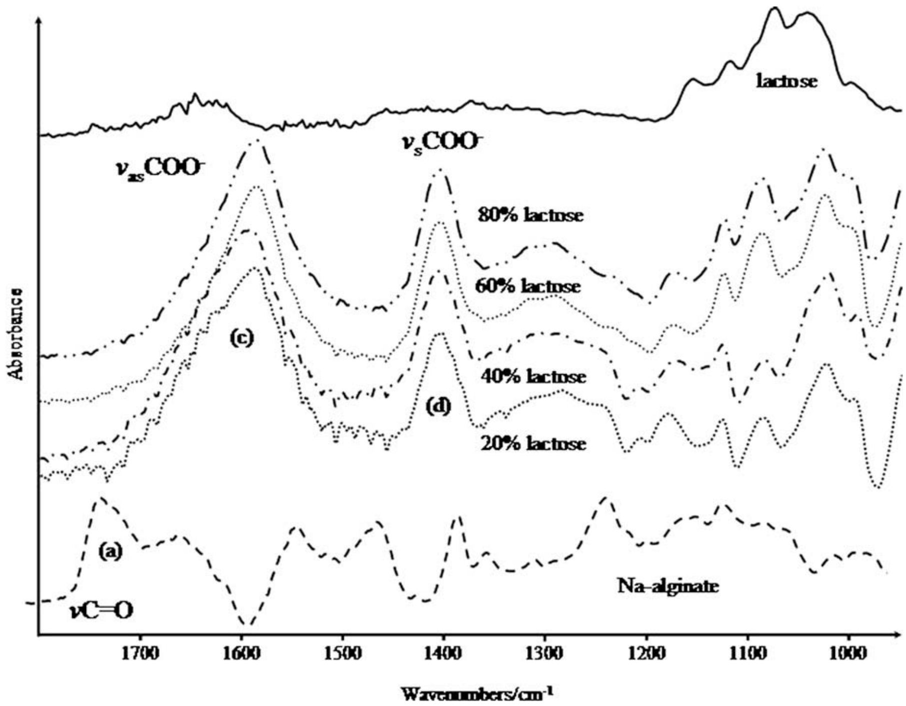

Fig. 4. Spectra resulting from the subtraction of the spectrum of the sodium alginate film from those of the lactose containing films. The bands at 1586 and 1405 cm^{-1} are characteristic of increasing amounts of carboxylate (COO$^-$) groups.

acid and the added lactose helps deprotonate the carboxylic groups of the polymeric acid. The accumulation of charged groups on the chain loosens the random coil because of the increasing repulsive forces, while the sodium ions, providing electric neutrality to the solution, stay in hydrated form in the interstitial space of the random coils. On the other hand, the addition of small molecules can fill the gaps between the macromolecules and also shield the electrostatic forces. These two opposite effects may be responsible for the minimum in the free volume of the film at ~40% lactose concentration.

4. Conclusions

It may be concluded that sodium alginate films are predominantly elastic. The presence of lactose in this film did not change the basic nature of the deformation, but the breaking force was decreased, in parallel with the increasing proportion of lactose.

The free volume of the polymer matrices was influenced by the composition of the samples, displaying a minimum at ~40% lactose content. Up to this concentration, the lactose can fill the holes in the polymer matrix. At higher ratios, the lactose is the predominant component and the structure of the polymer network becomes weaker. The beneficial effect of a high concentration of lactose in the alginate film on the dissolution of the spray-dried product can be explained by this weaker structure. This layer dissolved more quickly than the dense alginate film (which is know to have a gel-forming property). The rapid dissolution of this film can induce the surface erosion of a poorly-soluble component, and it can be a barrier to the aggregation of these particles in aqueous media. Consequently, the active agent can be liberated more quickly.

Study of the free volume of polymer matrices in combination with FT-IR experiments can furnish relevant information toward an understanding of the film-formation process. These data are very useful to explain the properties of the final coated products.

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