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Comparison of selected physico-chemical properties of calcium alginate films prepared by two different methods

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ABSTRACT

Sodium alginate (SA) is a naturally occurring, non-toxic, polysaccharide that is able to form gels after exposure to calcium. These gels have been used in food and biomedical industries. This is the first direct comparison of two different methods of calcium alginate film production, namely interfacial gelation (IFG) and dry cast gelation (DCG). IFG films were significantly thicker than DCG films, and were more extensively rehydrated in water and 0.1 M HCl than the DCG films. During rehydration in 0.1 M HCl almost all calcium ions were lost. Under scanning electron microscopy, IFG films appeared less dense than DCG films. IFG films were mechanically weaker than DCG films, and both types of film were weaker after rehydration in 0.1 M HCl compared with deionized water. Permeation of theophylline (TPL) was evaluated in-vitro; the diffusion coefficient (*D*) of the TPL was almost 90 times lower in DCG films than IFG films when both were rehydrated in water. Although the 0.1 M HCl rendered both gels more permeable to TPL, D of TPL was still about five times lower in DCG compared to IFG films. The evaluation of selected physico-chemical properties of films is important, since this information may inform the choice of gelation technique used to produce calcium alginate coatings on pharmaceutical products.

1. Introduction

Alginic acids are a family of non-toxic, water-soluble, linear hetero-polysaccharides composed of (1→4) linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, assembled into 'blocks' of homopolymeric domains (M-blocks and G-blocks) and regions of alternating residues (MG-blocks) (Dettmar et al., 2011; Draget et al., 1997; Haug et al., 1967; Smidsrød and Draget, 1996).

Ionic gels are prepared by introducing multivalent ions, such as Ca^{2+}, into a solution of, or over a film of, sodium alginate. These ions bind with G blocks, resulting in the crosslinking of G blocks in the alginate chains and leading to the formation of a three-dimensional, water-insoluble, gel network (de Celis Alonso et al., 2010; Smidsrød and Skjåk-Bræk, 1990).

The gel-forming property of sodium alginate has several biomedical and biotechnological applications, with alginate being employed as a gel matrix to encapsulate proteins, DNA and cells (Draget and Taylor, 2011; Gombotz and Wee, 1998) and to control the release of drugs (Augst et al., 2006; Dettmar et al., 2011; Rubio and Ghaly, 1994). In addition, polymer or polysaccharide derivative film coatings have found applications in taste masking and moisture protection (Joshi and Petereit, 2013), oral colonic delivery (Maroni et al., 2013a) and oral pulsatile release (Maroni et al., 2013b). Alginate gel films are also utilized in the food industry as edible films on fruits and vegetables (Arzate-Vázquez et al., 2012) and as coatings designed to improve stored meat quality (Krochta et al., 1994). In the pharmaceutical industry, alginate has recently been investigated as an excipient in vaginal film dosage forms (Machado et al., 2013). Furthermore, the use of alginate gel films as coatings for sustained drug release has also been explored (Bhagat et al., 1994; Sriamornsak and Kennedy, 2007) and is of interest in the present study.

Dry-cast gelation (DCG) and interfacial gelation (IFG) are two methods that have been employed to produce ionic gel films. In DCG, a solution of sodium alginate is evaporated to form a dry film that is subsequently exposed to an external source of cross-linking ion, such as an aqueous solution of calcium chloride (Aslani and Kennedy, 1996; Chan et al., 2006; Julian et al., 1988; Lim and Kennedy, 1997). In IFG, a solution of sodium alginate is separated from a solution of cross-linking ion by a selectively permeable membrane. The cross-linking ions diffuse uni-directionally through the membrane resulting in gelation of the alginate (Bhagat et al., 1994; Sriamornsak and Kennedy, 2006).

When gelation by calcium ions occurs, the cross-links that form between the alginate polysaccharide molecules would be expected to reduce their mobility and therefore limit their ability to extend

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upon rehydration (Kong et al., 2007). Both of these behaviors would be expected to impede the free diffusion of a drug molecule through the gel (Amsden, 1998). If the association between the alginate molecules in the network structure can be controlled using a particular gelation technique, there may exist a means to modify the release of a drug from a dose-form by employing a calcium alginate gel.

A key difference between the techniques of DCG and IFG is that the former involves producing a dry film of sodium alginate before it is gelled whereas the latter involves producing calcium alginate gel films in-situ within the SA solution. It is hypothesized that DCG would produce denser films than IFG, since drying the sodium alginate solution would promote entanglement of the polymer chains before they are gelled. Upon gelation, this entanglement would be 'locked in'. In contrast, during IFG, the calcium ions cause cross-linking of alginate molecules in solution. Conceivably, this would lead to the formation of gels in which the polymer chains are less tightly associated. When these gels are dried, the cross-links already formed may reduce the ability of the gels to become as dense as the DCG films. Consequently, it is hypothesized that the DCG technique would produce significantly less permeable gel films compared with the alternative technique, as a denser gel molecular structure would result in greater impediment to drug diffusion.

Calcium alginate gels prepared by diffusion of calcium ions through a membrane into a solution of alginate (akin to the IFG technique) was reported to result in non-homogeneous gels, with higher polymer concentration at the periphery compared to the center of the gel (Skjåk-Bræk et al., 1989). It is expected, therefore, that the alginate molecules would be more uniformly distributed in DCG films than IFG films because the alginate molecules in DCG films are condensed into a dried sheet before gelation. Differences in homogeneity may influence the relative permeability of the two film types.

Therefore, the aims of this work are to produce alginate gel films employing the two techniques, but with the same batch of sodium alginate and using a protocol that matches the different steps in the two processes as closely as possible. Then various physico-chemical characterization tests will be performed to see if there are differences between the film types. The tests will include thickness, calcium content, mechanical properties, morphology, and partitioning and diffusion of a model drug, theophylline. From these results, it may become apparent that one technique is more suitable for a given application such as sustained drug release.

2. Experimental materials and methods

2.1. Materials

Sodium alginate (SA) was purchased from the Sigma Chemical Company (USA); the medium viscosity grade was employed as received. This grade of SA is derived from *Macrocystis pyrifera*, and is known to have a high content of mannuronic acid ($F_M \sim 0.69$ and long G blocks; (Moe et al., 1995; Panikkar and Brasch, 1996)). The moisture content of the SA was determined by heating the powder to a constant weight at 105 °C (Sartorius model MA40, Germany); three measurements were made on the well-mixed contents of a single stock jar. Theophylline was obtained from the Sigma Chemical Company (USA) and calcium chloride (Biolab P.L., Australia), sodium citrate (Merck P.L., Australia) and concentrated hydrochloric acid (Ajax Finechem P.L., Australia) were of analytical reagent grade. Calcium carbonate (Pharmascope P.L., Australia) was of pharmacopoeial grade and deionized water was used throughout (model 08-4112, TKA Water Purification Systems, Germany).

2.2. Sodium alginate solution preparation

All solutions of 2% w/w SA were prepared by stirring the required weight of SA powder (adjusted for moisture content) in deionized water for 3–4 h at about 800 rpm at 25 °C, using a motorized stirrer with propeller blade (IKA Labortechnik, Germany). Once the SA solution was made to weight, it was stored undisturbed for 12–15 h in a refrigerator and then 3 h at 25 °C prior to further work. Triplicate rheograms of the 2% SA solution were obtained at 20 °C using a rotational viscometer with cone and plate geometry (model V88, Bohlin, Germany; cone diameter 30 mm and cone angle 5°). The flow behavior of the SA solution was determined using the Ostwald–de Waele equation, (Eq. (1)), where σ and γ are the shear stress and shear rate, respectively.

$$\sigma = K \times \gamma^n \quad (1)$$

A value of $n < 1$ for the flow behavior index, implies the solution displays pseudoplastic flow behavior and K is an estimate of the viscosity of the solution at a shear rate of 1 s^{-1}.

2.3. Preparation of gel films

Calcium alginate films were prepared by two techniques, namely DCG and IFG. The methodologies employed have been published previously; DCG (e.g., Julian et al., 1988; Aslani and Kennedy, 1996; Lim and Kennedy, 1997) and IFG (Sriamornsak and Kennedy, 2006, 2008). Although these techniques have been independently established in the literature, this study is the first direct comparison of the two film manufacturing methods.

2.3.1. Dry cast gel films

Initially, 1200 g of a 2% w/w sodium alginate solution was poured into a Perspex™ tray (50cm × 40 cm i.d.) which was leveled (Niveau-Level, model 61R, EDA, France). Any air bubbles created during pouring were gently drawn off or broken by Pasteur pipette. The SA solution, which filled the tray to a depth of about 6 mm, was allowed to evaporate at 25 °C and an average relative humidity (monitored by Tiny Tag Ultra, Gemini Data Loggers, UK) of 35% to form a dried sheet of sodium alginate after about 12 days. While the solution was evaporating, the tray was covered with a Perspex™ roof (12 cm above the surface of the solution) with open sides to allow airflow. The dried sheet was lifted from the tray and cut into squares, which were stored in a desiccator containing silica gel beads for 28 days prior to use.

Cut pieces of dried SA were converted to calcium alginate gel films by stirring them continuously at about 200 rpm, at 25 °C, for 1 h in 0.34 M aqueous calcium chloride. The volume of solution that the dried sodium alginate pieces were exposed to was dependent on the size of the piece; 200 mL of solution was used for each of the large pieces (70mm × 70 mm) whereas only 50 mL of solution was used for the small pieces (35mm × 35 mm). After 1 h of gelation, the calcium alginate gel films were removed from the solution, rinsed with deionized water and gently surface-dried with absorbent paper towel.

2.3.2. Interfacial gel films

The method used to prepare interfacial gel films was based on the novel gelation technique developed by Sriamornsak and Kennedy (2006). A cylindrical polypropylene mold (12.6 cm i.d., 7 cm high and with open top and bottom) had dialysis membrane (molecular weight cut-off 12,000–14,000, SpectraPor USA) held tightly across one of the open ends. The mold, containing 33 g of SA solution, was gently placed, membrane-side down, on to triangular spacers in a leveled 40cm × 50 cm Perspex™ bath containing 4 L of