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Gelatine enhances drug dispersion in alginate bilayer film via the formation of crystalline microaggregates

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ABSTRACT

In our previous study, a novel alginate-based bilayer film for slow-release wound dressings was successfully developed. We found that alginate alone yielded poor films; however, the addition of gelatine had significantly enhanced the drug dispersion as well as the physical properties. Here, an investigation of the drug–polymer interactions in the bilayer films was carried out. Drug content uniformity test and microscopy observation revealed that the addition of gelatine generated bilayer films with a homogenous drug distribution within the matrix. The FTIR and XRD data showed an increase in film crystallinity which might infer the presence of drug–polymer crystalline microaggregates in the films. DSC confirmed the drug–polymer interaction and indicated that the gelatine has no effect on the thermal behaviour of the microaggregates, suggesting the compatibility of the drug and excipients in the bilayer films. In conclusion, the addition of gelatine can promote homogenous dispersion of hydrophobic drugs in alginate films possibly through the formation of crystalline microaggregates.

1. Introduction

An ideal wound dressing provides rapid wound healing at a reasonable cost and with minimal discomfort for the patient (Acton, 2007; Abdelrahman and Newton, 2011). Conventional wound management formulations such as creams and gels are unable to maintain an effective drug concentration at the wound site due to a short residence time. Hydrocolloid film dressings are moisture-retaining dressings that contain gel-forming agents. When these dressings come in contact with wound exudates, the hydrocolloids absorb liquid and form a gel, promoting moist wound healing (Huang et al., 1999; Acton, 2008).

Alginate is a highly versatile biopolymer that has myriad pharmaceutical applications, including its uses as a gelling agent, thickener and stabiliser (Dong et al., 2006; Boateng et al., 2008). The alginate polymers are a family of unbranched linear polysaccharides that contain varying amounts of 1,4′-linked β-D-mannuronic acid and α-L-guluronic acid (G) residues. These polysaccharides are high molecular weight linear copolymers (approximately 5×10^5 Da) that are derived from sea weed and are normally present as sodium salts that are called sodium alginate. Sodium alginate forms an anionic polymer when the carboxyl groups on the uronic acid residues ($pK_a \sim 3.5$) dissociate in water. At high concentrations (≥5%, w/v), polyanionic sodium alginate chains begin to entangle and swell. This process increases the extension of the chains, thus producing a stable viscous hydrogel. Extension of the chain creates a diffusion barrier that in turn decreases the migration of small molecules such as drugs. As a result, alginate is often exploited as a controlled-release vehicle in drug delivery systems (Shu and Zhu, 2002; Dong et al., 2006).

Gelatine is denatured collagen that contains a triple helical superstructure of extended polypeptide chains. Gelatine contains free carboxyl and amino groups on its backbone and carries a positive charge in aqueous solution. Moreover, the presence of a gelatine backbone favours compact and ordered chain packing (Coviello et al., 2007). Gelatine-based biomaterials have been applied to artificial skin, bone grafts and scaffolds in tissue engineering. Gelatine has also been widely used in wound dressing materials and slow-release systems. This molecule has film-forming properties and is known to promote wound healing by preventing fluid loss due to exudation. Despite this film forming property, gelatine is rarely used alone due to its low intensity and high brittleness. Therefore, gelatine is often used after modification through several methods, such as cross-linking, grafting and blending (Shu and Zhu, 2002; Coviello et al., 2007). It is well known that blending is effective and convenient way to improve the performance of polymer materials (Dong et al., 2004; Coviello et al., 2007). The alginate/gelatine polyelectrolyte complex has recently received attention in slow drug delivery (Li et al., 2011). Sodium alginate and gelatine both have wound healing properties, and the combination of these two polymers and incorporation of drugs into these composite hydrocolloids may improve wound healing activity.

Our research group previously developed an alginate-based bilayer hydrocolloid film that is composed of an upper layer

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Table 1a
Formulations of the SA single layer films S1–S4.

Formulation code	SA (g)	Ibuprofen (g)	PG (mL)	Ethanol (mL)	Glycerol (mL)	Gelatine (g)	D.W. (mL)
S1	6	–	–	–	6	–	94
S2	6	5	15	5	6	–	74
S3	6	–	–	–	6	4	94
S4	6	5	15	5	6	4	74

impregnated with a model drug (ibuprofen) and a drug-free lower layer that acts as a rate-controlling membrane. The bilayer shows a slow drug release profile in vitro and exhibits accelerated wound healing compared to the controls in a wounded mouse model (Thu et al., 2012). The dispersal of hydrophobic drugs such as ibuprofen (log *P* 3.5) into an aqueous-based hydrogel usually requires the addition of co-solvents or solubilising agents. An ideal film dressing is required to be supple, possess homogeneous and smooth surfaces (Boateng et al., 2009). We observed that alginate alone produces poor (non-homogenous, rough surface and inflexible) bilayer films during the pre-formulation stage of bilayer film development. However, drug dispersion and the physical properties of the bilayer films were significantly enhanced by the addition of gelatine into bilayer films. This study was conducted to further investigate the effect of gelatine and the drug–polymer interactions that occur between the model drug ibuprofen and the alginate/gelatine hydrocolloid film. Drug content uniformity, scanning electron microscopy, X-ray diffraction, FTIR and DSC were conducted to assess the alginate-based bilayer formulations and compare the properties of the bilayers to that of the single layers (controls).

2. Materials and methods

2.1. Materials

Sodium alginate, ibuprofen, gelatine (from bovine skin, Type B) sodium dihydrogen orthophosphate were purchased from Sigma–Aldrich (Malaysia). Sodium hydroxide, sodium chloride, potassium dihydrogen orthophosphate, 99% (v/v) ethanol and glycerol were from Merck Chemicals (Malaysia). Propylene glycol was from R & M chemicals (U.K.). Cellulose acetate membrane with a 0.45 μm pore size was sourced from Sterzlitech Corporation (USA). All of the chemicals were analytical grade, and distilled water was used throughout the study.

2.2. Film preparation

The single and bilayer films were prepared as described in our previous study (Thu et al., 2012).

2.2.1. Single layer films

Sodium alginate, SA, single layer film formulations S1 and S2 were prepared (Table 1a). For the S1 single layer blank film formulation, 6.03 ± 0.02 g of SA powder was initially weighed. The SA powder was dissolved in 94 mL distilled water, which was gradually heated to 40 °C on a hot plate until a uniform solution was obtained. The beaker was removed from the heat when the solution reached 40 °C, and the solution was cooled and continuously stirred until a uniform gel was obtained. Then, 6 mL of glycerol was added into the SA gel as a plasticiser; the gel was stirred continuously during this process. The gel was then covered with parafilm and left to stand for approximately 10 min to remove the air bubbles that were trapped in the SA gel. For the S2 drug-loaded formulations, 5.03 ± 0.03 g of ibuprofen was dissolved in solutions containing different ratios of the co-solvents propylene glycol (PG) and ethanol, as shown in Table 1a. The SA gel was prepared with the same procedure used to prepare S1. Ibuprofen solution was added to the SA gel. The blank SA gel and drug-loaded SA gel were casted by pouring 12.5 ± 0.04 g of gel into clean, dry plastic petri dishes (area 58.05 cm^2). This gel weight was used because lesser volumes were not able to produce a satisfactory (i.e. smooth, homogenous and flexible) film. Thus, a casting volume of 12.5 g was selected. The gels were dried in an incubator at 37 °C and 50% relative humidity (RH) for 24 h. After 24 h, the casted films were weighed, covered with the lids of the plastic petri dishes and stored in desiccators containing silica gel beads at ambient temperature (25 ± 2 °C) until required.

Two SA/gelatine single layer film formulations (labelled S3 and S4) were prepared (Table 1a). For S3, 6.01 ± 0.02 g of gelatine powder was weighed and dissolved in 94 mL of distilled water (90 °C) until a clear and uniform gelatine solution was formed. Afterwards, 6.03 ± 0.03 g of SA powder was added into the gelatine solution at 40 °C. Then, 6 mL of glycerol was added to the SA/gelatine solution as a plasticiser. The solution was continuously stirred and cooled until a uniform SA/gelatine gel was obtained.

For S4, 5.03 ± 0.03 g of ibuprofen was dissolved in the co-solvents PG and ethanol. Then, the ibuprofen solution was added to the SA/gelatine gel. All of the SA/gelatine formulations were cast by pouring 12.5 ± 0.03 g of gel into clean plastic petri dishes with an area of 58.05 cm^2. The SA/gelatine single layer films were dried in an incubator at 37 °C and 50% RH for 24 h. After 24 h, the films were weighed, covered with the lids of the plastic petri dishes and stored in a desiccator containing silica gel beads at room temperature (25 ± 2 °C) until required.

2.2.2. Bilayer films

Bilayer films were prepared with a two-step technique. The bottom film layer was cast first and the second layer was then cast on top of the first dried layer. Here, four bilayer film formulations (identified as B1–B4) were prepared (Table 1b). Formulations B1 and B2 were prepared as blank bilayer films, whereas formulations B3 and B4 were prepared as drug-loaded bilayer films in which

Table 1b
Formulations of the bilayer films B1–B4.

Formulation code		SA (g)	Ibuprofen (g)	Gelatine (g)	PG (mL)	Ethanol (mL)	Glycerol (mL)	D.W. (mL)
B1	(Upper layer)	6	–	–	–	–	6	94
	(Lower layer)	6	–	–	–	–	6	94
B2	(Upper layer)	6	–	4	–	–	6	94
	(Lower layer)	6	–	4	–	–	6	94
B3	(Upper layer)	6	5	–	15	5	6	74
	(Lower layer)	6	–	–	–	–	6	94
B4	(Upper layer)	6	5	4	15	5	6	74
	(Lower layer)	6	–	4	–	–	6	94