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Alginate based bilayer hydrocolloid films as potential slow-release modern wound dressing

Hnin-Ei Thu, Mohd Hanif Zulfakar, Shiow-Fern Ng*

Drug Delivery and Novel Targeting Research Group, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 53000, Kuala Lumpur, Malaysia

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ABSTRACT

The aims of this research were to develop a novel bilayer hydrocolloid film based on alginate and to investigate its potential as slow-release wound healing vehicle. The bilayer is composed of an upper layer impregnated with model drug (ibuprofen) and a drug-free lower layer, which acted as a rate-controlling membrane. The thickness uniformity, solvent loss, moisture vapour transmission rate (MVTR), hydration rate, morphology, rheology, mechanical properties, *in vitro* drug release and *in vivo* wound healing profiles were investigated. A smooth bilayer film with two homogenous distinct layers was produced. The characterisation results showed that bilayer has superior mechanical and rheological properties than the single layer films. The bilayers also showed low MVTR, slower hydration rate and lower drug flux *in vitro* compared to single layer inferring that bilayer may be useful for treating low suppurating wounds and suitable for slow release application on wound surfaces. The bilayers also provided a significant higher healing rate *in vivo*, with well-formed epidermis with faster granulation tissue formation when compared to the controls. In conclusions, a novel alginate-based bilayer hydrocolloid film was developed and results suggested that they can be exploited as slow-release wound dressings.

1. Introduction

Wound healing is defined as body's replacement injured tissues with living tissues. It is a dynamic and intricate process which involve multiple cellular and matrix components act together to restore the integrity of injured tissue. The primary goals of wound care are rapid wound closure and leave minimal or aesthetically acceptable scar. Wound management is important in providing optimum healing milieu for wound healing (Sharman, 2003; Ovington, 2007). Depending on the severity of the wound, the desirable wound dressing may therefore serve among the purposes of (a) to provide moisture and occlusion, (b) protection from infections and contamination, (c) debridement, and (d) easy application and removal avoiding dressing-related trauma (Atiyeh et al., 2005; Singer and Dagum, 2008; Abdelrahman and Newton, 2011). Occasionally, drug-loaded wound dressings are used to treat wound locally such as anti-infections due to secondary infection or for pain control, especially in chronic wounds (Lawrence, 1994; Steffansen and Herping, 2008; Fouda et al., 2009).

Various wound care products are available in the wound care management market and they are targeted towards the treatment of both acute and chronic wounds (Abdelrahman and Newton, 2011). Among the modern wound dressings, dressings cast from hydrogels, sometimes know as hydrocolloid dressings, have been developed and uses as the first major advances in moist wound management. Wound healing is promoted by dressings that maintain a moist environment. Hydrocolloid has the ability to form gels upon contact with wound exudates and the high absorption occurs via strong hydrophilic gel formation (Lanel et al., 1997). The formation of gel allows excess fluid to escape without permitting wound desiccation. However, the fluid handling capacity of hydrocolloid dressings depends on many factors such as the physicochemical properties and the design of the dressing.

Alginate, a natural polymer, is used in the fabrication of hydrocolloid film wound dressings due to its biocompatibility, biodegradation and excellent film forming properties (Thomas, 2000; Balakrishnan et al., 2005). Sodium alginate is a water-soluble salt of alginic acid, a naturally occurring polysaccharide found in the cell wall of brown algae. It contains two uronic acids, β-(1-4)-linked D-mannuronic acid (M) and α-(1-4) linked L-guluronic acid (G), and is composed of homopolymeric blocks M–M or G–G, and blocks with an alternating sequence of M–G blocks. The various degree of crosslinking will reduce significantly the hydrogel swelling in the presence of the water, causing the release of drugs within the alginate matrices will be delayed. As a result, alginate is often being exploited as a drug controlled release vehicle in drug delivery systems (Pepperman et al., 1991; Shu and Zhu, 2002; Dong et al., 2006; Wang et al., 2010b). As wound dressings, alginate hydrogels

* Corresponding author. Tel.: +60 3 9289 7977; fax: +60 3 9289 7060.
E-mail address: nsfern@gmail.com (S.-F. Ng).

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Table 1
(a) Formulations of the single layer films S1–S5 and (b) formulations of bilayer films B1and B2.

(a)

Formulation	Sodium alginate (g)	Ibuprofen (g)	Propylene glycol (mL)	Ethanol (mL)	Glycerol (mL)	Distilled water (mL)
S1	6	5	10	5	6	79
S2	6	5	15	5	6	74
S3	6	5	20	5	6	69
S4	6	5	25	5	6	64
S5	6	5	30	5	6	59

(b)

Formulation	Sodium alginate (g)	Ibuprofen (g)	Gelatin (g)	Propylene glycol (mL)	Ethanol (mL)	Glycerol (mL)	Distilled water (mL)
B1							
Upper layer	6	5	–	15	5	6	74
Lower layer	6	–	–	–	–	6	94
B2							
Upper layer	6	5	4	15	5	6	74
Lower layer	6	–	4	–	–	6	94

can retain and create a moist environment around the wound to promote wound healing (Boateng et al., 2008).

Previously, research has shown that composite films have improved physical, transport and mechanical properties compared to those of single component-based films (López-Caballero et al., 2005; Chiono et al., 2008; Rivero et al., 2009; Gómez-Estaca et al., 2010; Wang et al., 2010a; Pereda et al., 2011). The term 'bilayer film' was described by Rivero et al. (2009) as two hydrocolloid layers, one cast over another. Recently, bilayer composite film systems based on various biopolymers are extensively investigated in food technology and bioengineering applications as edible films due to their better mechanical properties, higher moisture retaining properties and ease of preparation relatively to other film formulation. (Chiono et al., 2008; Rivero et al., 2009; Pereda et al., 2011). However, little is known on bilayers in wound healing and drug delivery applications.

In this study, an alginate-based bilayer film formulation was developed and investigated for its potential as slow-release wound healing vehicle. A model drug (ibuprofen) was loaded onto the upper layer while the drug-free lower layer was acted as a rate-controlling membrane. Ibuprofen was chosen because it is used as an effective adjunct in wound pain management for reducing pain during dressing changes. Jørgensen et al. (2006) evaluated the efficacy and pain reduction of Biatain®-Ibu, a new commercial wound dressing containing ibuprofen on patients with chronic leg ulcer wound pain. They concluded that ibuprofen could reduce persistent and temporary chronic leg ulcer wound pain, thus increase patients' quality of life. The aims of this research were to characterise alginate–gelatin bilayer film in terms of thickness, solvent loss, moisture vapour transmission rate, expansion rate, rheological and mechanical properties. The surface and cross-sectional morphology was examined using scanning electron microscopy and the *in vitro* drug release was conducted using Franz diffusion cells. The *in vivo* animal study was also undertaken to evaluate the effect of bilayer film formulations on full-thickness wound healing. All of the bilayer properties were compared to that of the single layer films.

2. Materials and methods

2.1. Materials

Sodium alginate (SA), ibuprofen and gelatin powder (from bovine skin, Type B) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Propylene glycol, 99% ethanol and glycerol were obtained from Merck (Germany). Ketamine hydrochloride, xylazine hydrochloride and formaldehyde were procured from Troy Laboratories (Australia). Haeris haematoxylin and eosin were obtained from Microm International (Germany). Distilled water was used throughout.

2.2. Pre-formulation

SA single layer films were first dried cast from the gel formulations in Table 1a, S1–S5, with varying amount of propylene glycol and ethanol. All films were prepared in a plastic petri dish with an area of 58.05 cm^2. To this end, 6 g of SA was stirred in distilled water until an uniform gel slurry was obtained at 40 °C. 5 g of ibuprofen was dissolved in 20 mL of propylene glycol and ethanol co-solvent of varying ratio shown in Table 1a. The ibuprofen solution was then added to the SA gel and stirred homogenously. Then, 6 mL of glycerol was added into the SA gel while stirred continuously. The prepared SA film was cast by pouring approximately 12.5 g of SA gel into the plastic petri dish. The SA gel was dried in incubator at 37 °C and RH 50% for at least 24 h. The dried SA film was stored at room temperature.

2.3. Preparation of bilayer hydrocolloid films

The most satisfactory film of S1–S5 based on appearance and physical characteristics was selected to formulate bilayer films. For the bilayer films, only the upper layer was loaded with model drug (ibuprofen). Here, S2 was chosen to proceed for bilayer film formulation. Two bilayer formulations, namely B1 and B2 were prepared (Table 1b). For B1 lower layer, 6 g SA powder was dissolved in distilled water and 6 mL glycerol was added. Instead of 12.5 g, 45 g of the SA gel was poured into petri dish and was dried as lower layer in an incubator at 37 °C and RH 50% for 72 h. As for B1 upper layer, the preparation method was similar to that of single layer S2. After the gel was prepared, 12.5 g of the gel containing ibuprofen was poured above the dried lower layer and the composite was then placed at 37 °C and RH 50% for further 72 h. To prepare the B2 lower layer, 4 g of gelatin powder was stirred in 94 mL distilled water at 90 °C. 6 mL of glycerol was added and stirred until a uniform gel was obtained. The SA/gelatin gel was cast as by pouring approximately 45 g onto the plastic petri dish. The lower layer film was dried in an incubator at 37 °C and RH 50% for 72 h. For the upper layer, the SA/gelatin gel mixture was prepared according to lower layer method above. Ibuprofen 5 g was dissolved in 20 mL of co-solvent of propylene glycol and ethanol of 15:5 ratios. The ibuprofen solution was then added into the SA/gelatin gel. Then, the 12.5 g prepared SA/gelatine gel containing ibuprofen was poured above the dried lower layer in the petri dish. The composite was then placed at 37 °C and RH