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# Development of polyvinyl alcohol–sodium alginate gel-matrix-based wound dressing system containing nitrofurazone

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ABSTRACT

Polyvinyl alcohol (PVA)/sodium alginate (SA) hydrogel matrix-based wound dressing systems containing nitrofurazone (NFZ), a topical anti-infective drug, were developed using freeze–thawing method. Aqueous solutions of nitrofurazone and PVA/SA mixtures in different weight ratios were mixed homogeneously, placed in petri dishes, freezed at −20 °C for 18 h and thawed at room temperature for 6 h, for three consecutive cycles, and evaluated for swelling ratio, tensile strength, elongation and thermal stability of the hydrogel. Furthermore, the drug release from this nitrofurazone-loaded hydrogel, in vitro protein adsorption test and in vivo wound healing observations in rats were performed. Increased SA concentration decreased the gelation%, maximum strength and break elongation, but it resulted into an increment in the swelling ability, elasticity and thermal stability of hydrogel film. However, SA had insignificant effect on the release of nitrofurazone. The amounts of proteins adsorbed on hydrogel were increased with increasing sodium alginate ratio, indicating the reduced blood compatibility. In vivo experiments showed that this hydrogel improved the healing rate of artificial wounds in rats. Thus, PVA/SA hydrogel matrix based wound dressing systems containing nitrofurazone could be a novel approach in wound care.


## 1. Introduction

A large number of dressings are currently used in the management of burns, split graft donor sites, chronic ulcers, decubitus ulcers, and so on (Dyson et al., 1991; Eaglstein and Pittsburgh, 1985; Suzuki et al., 1997; Tanihara et al., 1998). There are two kinds of dressings: dry type and wet type. It has been reported that healing with a wet environment is faster than that with a dry environment (Winter, 1962). In recent years, hydrogels have received considerable attention to be used as specific absorbents in wound dressing materials. Thus, a number of polymers with superabsorbent properties have been developed for clinical applications, such as liquefaction and removal of scar, treatment of leg ulcers, pressure sores, and prevention of tissue deterioration in patients with restricted mobility.

Polyvinyl alcohol (PVA) has several useful properties including non-toxicity, biocompatibility, high hydrophilicity, fiber/film forming ability, and the chemical and mechanical resistance. It has been widely commercialized and studied in the chemical and medical industries for the productions of fibers, films, coatings, cosmetics, pharmaceuticals, and so on (Yeo et al., 2000). PVA hydrogels produced by using the freezing–thawing technique form a matrix of physically crosslinked polymeric chains containing uncrosslinked polymer and water. The use of freeze–thawed PVA hydrogels has been explored for biomedical and pharmaceutical applications. These gels are non-toxic, non-carcinogenic, have good biocompatibility, and have desirable physical properties such as rubbery nature and high degree of swelling in water (Peppas and Stauffer, 1991). PVA must be crosslinked if it is to be used in biodegradable materials. PVA hydrogel has excellent transparency and is smooth as membrane, and it is also biologically inactive and bio-compatible. It has attracted much attention to be widely used as a good material for temporary skin covers or burn dressings (Peppas and Scott, 1992).

Alginate derived from brown algae is an anionic linear polysaccharide composed of 1,4-linked β-D-mannuronates residues and 1,4-linked α-L-guluronates in varying proportions (Rees and Welsh, 1997). Alginate is hydrophilic, biocompatible, and relatively economical. It has been widely used in medical application such as wound dressings, scaffolds for hepatocyte culture and surgical or dental impression material, even if the allergic reaction to skin

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has been occurred (Ng and Cheng, 2007; Patel, 1993). They have been successfully applied to cleanse a wide variety of secreting lesions. The high absorption is achieved via strong hydrophilic gel formation. This limit wound secretions and minimizes bacterial contamination. Alginate fibers trapped in a wound are readily biodegraded (Gilchrist and Martin, 1983). Alginate dressings maintain a physiologically moist microenvironment that promotes healing and the formation of granulation tissue. Alginate can be rinsed away by saline irrigation, thus the removal of the dressing does not interfere with healing granulation tissue. This makes dressing changes virtually painless. Alginate dressings are very useful for moderate to heavily exuding wounds (Motta, 1989). The importance of polymer blending has been increased in recent years because of the preparation of the polymeric materials with desired properties, low basic cost, and improved process ability. In this study, we attempted to use the sodium alginate as a component of PVA hydrogel for wound dressing.

## 2. Materials and methods

### 2.1. Materials

PVA (typical average $M_w$ = 146,000–186,000; +99% hydrolyzed), sodium alginate, nitrofurazone (5-nitro-2-furfural semicarbazone), human serum albumin (HSA) ($M_w$ = 66 kD, albumin: 97.31%) and human plasma fibrinogen (HPF) ($M_w$ = 341 kD, clottable proteins > 95%) were purchase from Sigma–Aldrich, Kanto Chemical Co. (Tokyo, Japan), Fluka Co. (Germany) and Calbiochem Co. (Germany), respectively. All other chemicals were used without any further purification.

### 2.2. Preparation of hydrogels

PVA/SA hydrogels were obtained by freezing–thawing (F–T) cycle (Peppas and Stauffer, 1991). Solutions containing 10% (w/v) PVA and 3% (w/v) SA and nitrofurazone were prepared in deionized water. Different proportions of PVA and SA (SA = 0, 5, 10, 20 and 30%) solutions were mixed by vortexing for an hour, and the calculated amounts of this mixture were poured in petri dishes, followed by freezing at −20 °C for 18 h and thawing at room temperature for 6 h, for three consecutive cycles.

### 2.3. Determination of gel fraction

After three F–T cycles, the samples were dried for 6 h in 50 °C in an oven ($W_0$), then soaked in distilled water for 24 h up to a constant weight (equilibrium swelling $W_s$) in order to remove the soluble parts. The gels were then dried again in 50 °C oven ($W_e$). The gelation% was then calculated by the following equation.

$$\text{Gelation}(\%) = \frac{W_e}{W_0} 100.$$

### 2.4. Determination of swelling ratio

To measure the swelling behavior, hydrogel samples were cut into 2 cm × 2 cm pieces and dried at 50 °C in an oven for 1 h and their dry weights ($W_e$) were immediately measured, then they were soaked in PBS maintained at 37 °C and their weights ($W_s$) were determined at specific time points and the swelling ratio (SR) was calculated using the following formula:

$$\text{SR}(\%) = \frac{W_s}{W_e} 100.$$

Changing of 20% (w/w) sample's weight was also observed for 30 min. To minimize error caused by surface water, weights after immediate soaking ($W_{si}$) were also taken. The swelling ratio was then determined according to the following formula (Balakrishnan et al., 2005; Choi et al., 1999).

$$\text{SR}(\%) = \frac{W_s - W_{si}}{W_e} 100.$$

### 2.5. Determination of the mechanical properties

The tensile strength and breaking elongation of hydrogels were determined using a tensile test machine (Instron 4464, UK). After three F–T cycles, the hydrogels were cut into specific dog bone shape (6 cm long, 2 cm wide at the ends and 1 cm wide in the middle). The mechanical analysis was performed at a stretching rate of 20 mm/min with pre-load of 0.5 N to determine the maximum load for each matrix. The thickness of each individual hydrogel was also measured (Alvaro Antonio Alencar et al., 2003; Lin et al., 2006; Wu et al., 2001).

### 2.6. Thermal analysis properties

The thermal analysis properties of hydrogels were determined using differential scanning calorimeter (DSC) (TA, USA). The samples were heated from room temperature to 300 °C. They were annealed for 2 min at this temperature and then cooled to 0 °C at the rate of 10 °C/min, and finally heated to 200 °C at a heating rate of 20 °C/min to obtain the crystallization temperature ($T_c$) and melting temperature ($T_m$). All the DSC measurements proceeded under the nitrogen flow of 10 ml/min. To determine the thermo-stability of blends, thermo gravimetric analysis (TGA) (TA, USA) was used with samples heated from 25 to 500 °C at a heating rate of 10 °C/min. Then, change of weights was observed (Lin et al., 2006).

### 2.7. Adsorption of protein onto hydrogel surface

Pieces of hydrogel membrane cut into 2 cm × 2 cm were immersed in 4 ml of pH 7.4 phosphate buffer solution (PBS) at 37 °C containing HSA and HPF proteins, and shaken at 100 rpm for 24 h. Samples were then gently taken out and rinsed five times with PBS, placed in six wells containing aqueous solution of 1% sodium dodecyl sulfate (SDS) and shaken for 1 h at room temperature to remove the protein adsorbed on the surface. The protein contents of the each sample were then measured using the Bradford reagent. The absorbance at 570 nm was measured using an ultraviolet spectrometer. The calibration curve was prepared by measuring varying protein concentrations in SDS solution (Alvaro Antonio Alencar et al., 2003; Lin et al., 2006).

### 2.8. Dissolution test

The drug release from hydrogel was measured by using Teflon frame instrument, as illustrated in Fig. 1. Only one side of sample was attached to the Teflon frame instrument that was immersed into 400 ml distilled water at 37 °C as the dissolution medium and stirred at the paddle speed of 50 rpm. One milliliter of the sample was withdrawn from the medium at various time intervals. The concentration of drug was determined by high-performance liquid chromatograph (PU-987 pump and UV-975 UV detector, Jasco). 50 μl of the samples were injected into the column (5 μm particle size, 4.6 mm × 150 mm, Inertsil C18, GL science) with a UV detector at 365 nm. The mobile phase was acetate buffer (pH 4.6)-acetonitrile (75:25, v/v) at 1 ml/min (Chung et al., 2003; Draisci et