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Elucidation of two water leachable polymers impact on microporous membrane performance and drug permeation

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ABSTRACT

The influence of two water-leachable pore-forming agents, polyvinylpyrrolidone (PVP) and poly(ethylene glycol) (PEG), on the performance of cellulose acetate (CA) microporous membranes was elucidated. Various compositions of CA/PVP and CA/PEG blended membranes were prepared and characterized by Fourier transform infrared (FTIR) spectroscope and differential scanning calorimetry (DSC). The FTIR data indicated the presence of interaction between CA and pore-forming agent via a hydrogen bond. The DSC thermal data implied that CA and PEG presented as two separated phases in the blended membranes. However, CA and PVP were miscible at the blended compositions. The extent of miscibility between CA and pore-forming agents dominated the leach degree of the latter. The microporous membranes prepared by solvent–casting–leaching showed that PEG was completely leached from CA/PEG blended membranes regardless of its initial blending level. On the contrary, the leach of PVP was dependent of the initial composition of CA/PVP blended membranes. The permeation of theophylline from CA/PEG microporous membranes was much faster than from CA/PVP ones especially when blending 40–50% pore-forming agent. Although the porosities of $CA_{50\%}/PVP_{50\%}$ and $CA_{50\%}/PEG_{50\%}$ microporous membranes were similar, less tortuosity and more interconnected channels in terms of higher ε/τ value of $CA_{50\%}/PEG_{50\%}$ microporous membrane resulted in the highest drug permeation. The permeation of theophylline through CA microporous membranes showed a good linear correlation with the ε/τ values of all microporous membranes ($r^2 = 0.994$).

1. Introduction

Many studies have demonstrated the advantages of sustained release dosage forms including employing less drug dose, minimizing side effect, and improving therapeutic efficacy etc. Among sustained release systems, orally controlled release systems receive the most attraction due to easy administration and better patient compliance [1]. CA is a semipermeable polymer with biocompatible property. It is water insoluble, pH insensitive, and not degradable in gastrointestinal tract. Nowadays, it is widely used in drug delivery system due to its low toxicity, good safety and low cost. CA has been applied in osmotic pump tablets where an orifice was drilled by laser beam to allow drug free penetration [2,3]. The new generation of controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules (e.g., sodium chloride, potassium chloride, urea, sucrose etc.) or water-soluble polymers into CA membranes to create pores [4–6]. The blending pore-forming agents avoids using high technique laser to drill the orifice for drug release and eliminates controlling drug release by single pathway [7].

This finding accelerates the development of polymer blends to produce microporous coating film for drug release. The blended membrane may include two types of polymers: one polymer is remained in the end-use, and another polymer is leachable as a pore-forming agent to produce micropores in the coating membranes. Ideally, the pore-forming agents are leached from the blended membranes in the body fluid or aqueous medium to create micropores for drug release. The microporous membrane has been successfully applied to control drug release from CA and ethylcellulose (EC)/hydroxypropyl methyl cellulose (HPMC) coated osmotic pump tablets followed a zero-order release mechanism [8]. The microporous membranes formed by leach of water-soluble plasticizers (e.g., propylene glycol) or water-insoluble plasticizers (e.g., castor oil) show different impact on drug release [9]. The similar concept has been applied to control porosity of the asymmetric membrane coated capsules via incorporating various types of compounds (e.g., glycerol, polyethylene glycol 400, and dibutyl phthalate) [10].

The application of pore-forming agents and plasticizers to produce microporous membranes to control drug release has been

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studied a lot [11–14]. However, how these molecules affecting microporous film morphology and drug permeation performance was seldom compared and elucidated. In our study, two widely used water-soluble polymers, PVP and PEG, were selected as pore-forming agents to blend with the major polymer CA. PEG is popularly used in pharmaceutical dosage forms. Recently, it is used to conjugate with liposomes and nanoparticles to prolong their blood circulation time *in vivo* [15–17]. The combination of PVP with synthetic polyacrylic acid derivatives shows excellent mucoadhesive property, which can be usefully applied in intestinal mucoadhesive dosage forms [18]. The impacts of the type and the blending level of pore-forming agent on micropore morphology and theophylline permeation performance were demonstrated from a series of CA microporous membranes, and the correlated relationship of both was established. Theophylline was chosen as a model drug for *in vitro* permeation study. Theophylline is usually used for treatment of asthma and chronic obstructive pulmonary disease. Its therapeutic concentration is narrow in the range of 5–15 μg/mL, and the side effect will be frequently occurred especially at concentration higher than 20 μg/mL. There are several sustained dosage forms for theophylline in the market, such as Theo-Dur® extended-release tablet, Uni-Dur® extended-release tablet, Theo-X™ extended-release tablet, and Theolair-SR® tablet etc.

2. Experimental

2.1. Materials

CA (MW 30,000) and theophylline anhydrous were from Sigma–Aldrich Co. (St. Louis, MO, USA). PVP (MW 10,000) was from Fluka Chemical Co., Inc. (Buchs, Switzerland). PEG (MW 4000) was from Waco Pure Chemical Ind. Ltd. (Osaka, Japan).

2.2. Preparation of blended membranes and microporous membranes

CA and various weight ratios of PVP or PEG (0, 10, 20, 30, 40, 50%, w/w) were co-dissolved in a mixture of acetone and ethanol in a volume ratio of 4:1. The polymer solution was cast on a plate and the solvent was evaporated at room temperature. The residual solvent was further evaporated at 37 °C in an oven for 48 h. The weight (W_0) of each blended membrane was measured and recorded. The microporous CA membranes were further prepared via a solvent–casting–leaching method. Each blended membrane was immersed in 100 mL deionized water and shaken at 100 rpm for 10 days. The medium was replaced every day to assure the leach of PVP and PEG as complete as possible. The leached membranes were dried at 37 °C for 48 h, and the microporous membranes were obtained. The weight (W_f) of each microporous film was measured and recorded.

2.3. Characterization of blended membranes

2.3.1. FTIR analysis

The samples were prepared by casting various compositions of blended polymer solutions of CA/PVP and CA/PEG on KBr salt disks. The blended polymeric membranes were obtained after solvent evaporated. They were analyzed with a FTIR spectrophotometer (FT/IR-410, JASCO, Tokyo, Japan). The FTIR spectra were recorded over the range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1} for 100 scans.

2.3.2. DSC analysis

The melting temperature (T_m), heat of fusion (ΔH_f), heat capacity ΔC_p, and glass transition temperature (T_g) of blended membranes were determined using a DSC (Diamond DSC, Perkin Elmer Instruments Co., Ltd., USA). Samples (~5 mg) were heated to 250 °C at 10 °C/min (first run), and the T_m as well as the ΔH_f were determined from the DSC endotherms. For measurement of the T_g, the samples were cooled to room temperature then reheated to 250 °C at a heating rate of 10 °C/min (second run). The T_g was taken at the midpoint as the heat capacity changed. The measured T_g and ΔC_p of CA and PVP were further applied into Fox equation (Eq. (1)) to predict the T_g values of CA/PVP blended membranes [19].

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \quad (1)$$

W_1: weight ratio of CA; W_2: weight ratio of PVP; T_{g1}: glass transition temperature of CA; T_{g2}: glass transition temperature of PVP; T_g: glass transition temperature of a CA/PVP blended membrane

2.4. Characterization of microporous membranes

2.4.1. Thickness and morphology

The thickness of microporous membranes after leaching of pore-forming agent in aqueous medium was measured with a caliper (SM-114, Teclock Instruments Co., Ltd., Japan). The morphology of microporous membranes was observed with a scanning electron microscope (JSM-6300 JEOL, Japan). The microporous membrane was coated with gold/palladium under an argon atmosphere, and the vertical cross-section and the surface morphology of microporous membranes were observed.

2.4.2. Leaching extent and porosity

The percentages of PVP and PEG leached from the blended membranes were calculated according to the following equation:

$$\text{PVP or PEG leached}(\%) = \frac{W_0 - W_f}{\text{initial blending weight of PVP or PEG}} \times 100\% \quad (2)$$

where W_0 and W_f were the weights of membranes before and after leaching process. The porosity (ε) of CA microporous membranes blended with various weight ratios of PVP or PEG was calculated according to Eq. (3) [20].

$$\varepsilon = 1 - \frac{W_{CA}/\rho_{CA} + W/\rho}{V_T} \quad (3)$$

W_{CA}: the weight of CA in the microporous membrane; W: the weight of PVP or PEG left in the microporous membrane; ρ_{CA}: the density of CA; ρ: the density of PVP or PEG; V_T: the volume of membrane.

2.5. Permeation study

Permeation experiment was performed by using a horizontal side-by-side diffusion cell at 37 °C. Microporous membranes, previously equilibrated in deionized water overnight, were clamped between two compartments of diffusion cells. The theophylline solution (5 mg/mL) was placed in the donor compartment. All of the sample solution was taken from the receiver compartment at each predetermined interval, and equal volume of fresh medium was replaced. Both donor and receiver compartments were stirred continuously throughout the experiments. The concentration of theophylline was determined by spectrophotometer at 272 nm (Hitachi U-2001, Hitachi Co., Ltd., Tokyo, Japan). The drug permeation was defined as follow,

$$\frac{dM}{dt} = \frac{DSKC_d}{h} = PSC_d \quad (4)$$

where M is the amount of drug permeated at time t; D is the diffusion coefficient; S is the effective diffusion area; K is the partition