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Integrating sol–gel with cold plasmas modified porous polycaprolactone membranes for the drug-release of silver-sulfadiazine and ketoprofen

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ABSTRACT

A controlled release system composed of surface modified porous polycaprolactone (PCL) membranes combined with a layer of tetraorthosilicate (TEOS)–chitosan sol–gel was reported in this study. PCL is a hydrophobic, semi-crystalline, and biodegradable polymer with a relatively slow degradation rate. The drugs chosen for release experiments were silver-sulfadiazine (AgSD) and ketoprofen which were impregnated in the TEOS–chitosan sol–gel. The surface modification was achieved by O_2 plasma and the surfaces were characterized by water contact angle (WCA) measurements, atomic force microscope (AFM), scanning electron microscope and electron spectroscopy for chemical analysis (ESCA). The results showed that the release of AgSD on O_2 plasma treated porous PCL membranes was prolonged when compared with the pristine sample. On the contrary, the release rate of ketoprofen revealed no significant difference on pristine and plasma treated PCL membranes. The prepared PCL membranes showed good biocompatibility for the wound dressing biomaterial applications.

1. Introduction

Poly(ε-caprolactone) (PCL) is a hydrophobic, semi-crystalline, and biodegradable polymer that possesses great potentials for biomedical applications [1] and for the developments of drug/vaccine delivery vehicle [2] due to its good permeability and low toxicity. However, due to the very slow *in vivo* degradation rate, the modifications of PCL membranes were achieved by copolymerization [3,4] or blending [5,6] with other polymers. Polyethylene glycol (PEG) is one of the important biomedical polymers that exhibits excellent antifouling properties [7,8]. Moreover, the blending of PCL with PEG resulted in microporous membranes that provide excellent control on the release of drug molecules with small and moderate size [6].

Sol–gel technology has drawn extensively research interests for the preparation of inorganic–organic composite materials because it effectively overcame the problem of brittleness of inorganic sol gel that it was utilized to prevent the contamination of electroanalysis, to avoid the analyte preconcentration in electrochemical detection [9], and to assist the formation of thin film for gas sensor fabrication [10]. Tetraorthosilicate (TEOS) based SiO_2 sol–gel is formed by hydrolysis-condensation route in acidic condition [11,12]. Chitosan is a polycationic natural polymer and its biodegradability, nontoxicity and biocompatibility makes it a promising matrix for enzyme immobilization and for clinical application [13–15]. It was reported that chitosan–SiO_2 sol–gel demonstrated a highly porous microstructure with an excellent performance for enzyme immobilization [16,17] and for drug release [18–20].Ketoprofen is a non-steroidal anti-inflammatory agent for analgesic and antipyretic but exhibits undesirable renal and gastric side effects [21]. Therefore, drug delivery for ketoprofen through skin (topical administration) is considered more advantageous when compared to oral and intravenous delivery. The effective formulation of topical administration is essential to inhibit edema [22], to minimize the production cost [23], and to overcome the water-solubility issue [24]. Silver sulfadiazine (AgSD), being able to release silver ion to obstruct the DNA of microorganisms, is an effective antimicrobial agent for preventing the infections on burn wounds. The standard 1% AgSD cream which involves frequent application associated the problem of increase wound trauma and thus postponed the wound healing [25]. Moreover, a high dose of silver ions may trigger intoxication [26]. It is therefore imperative to design an appropriate system that assists the controllable release of ketoprofen and AgSD. Gallagher et al. [27] utilized hydroxypropyl cellulose gel containing ketoprofen in nylon films for drug release tests for a 24 h period with the largest cumulative release of about 3300 μg/cm^2. Yu et al. [28] used ion-exchange fiber gel to load ketoprofen and performed the release through fiber membrane where the largest cumulative release rate of 40% was obtained at 8 h release time. Paolino et al. [29] incorporated ketoprofen into lecithin-based emulsion cream to study the release through skin and obtained the largest cumulative release

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of ~114 μg/cm^2 for a release period of 24 h. Ketoprofen and fatty acid ester mixture was applied for drug release tests through mouse skin over 10 h release by Fujii et al. [30], with the largest cumulative release of about 500 μg/cm^2. Moreover, hydroxypropyl cellulose gel was also utilized for ketoprofen release over 48 h period and about 91% cumulative release was reached [31]. In the present work, the *in vitro* release of AgSD and ketoprofen encapsulated in sol–gel under a PCL barrier membrane was determined by using Franz diffusion cells [32–34].

In this study, ketoprofen and silver sulfadiazine were chosen as model drugs and were incorporated by the hybrid sol–gel/membrane platform (chitosan–SiO_2/PCL) where the sol–gel played the role of biodegradable layer for drug entrapment and the PCL membranes served as a barrier for controlling the release rate. The results showed that the ketoprofen release rate was similar for the systems using pristine and plasma treated PCL membranes but with lower cumulative release amount on those applying the plasma treated PCL barriers. On the contrary, the release of AgSD was effectively retarded by more than 4 days for the system using the oxygen plasma treated PCL membranes. Moreover, the oxygen plasma treated PCL membrane revealed excellent biocompatibility that the modified membrane systems is applicable for further applications such as wound healing dressing and tissue engineering scaffolds.

2. Materials and methods

2.1. Preparation of PCL membrane

PCL–PEG solution was prepared by mixing 10 g of PCL pellet (Sigma, MW 70,000–90,000) and 7.5 g of PEG (Sigma, MW 300), followed by the addition of 29 mL THF (Echo, 99.5%). The PCL–PEG solution was then casted on a PTFE plate using a custom made scraper, preceded with immediate immersion in a coagulant bath filled with 60% DI water and 40% acetone (Acros, 98%) for 10 min to remove the PEG, leading to formation of micropores. The casted PCL membranes were immersed in 4 °C DI water overnight to allow the evaporation of organic solvents. The thickness of the prepared PCL membrane was about 150 μm.

2.2. Preparation of drug sol–gel mixture

The sol–gel solution (2 wt%) was prepared by dissolving chitosan (Sigma, >75%) in 2% (v/v) acetic acid solution (Acros, 96%) and stirred for 2 h. In addition, 3 mL acetic acid solution was added into 3 mL tetraethylorthosilicate (TEOS, Acros, 98%) and stirred for 8 h. The chitosan–sol–gel-drug was prepared by dissolving 3 mg of ketoprofen (Sigma, 99%) or silver sulfadiazine (AgSD, Sigma, 98%) in 3 mL of phosphate buffered saline (PBS) solution (Sigma, P3813). The chitosan–sol–gel-drug was obtained by mixing 2.5 mL of the prepared chitosan solution with 2.5 mL of acidic TEOS solution and 2.5 mL of drug solution in a bottle under stirring at room temperature.

2.3. Plasma treatments on PCL membranes

PCL membrane was cut to 2.5 cm × 2.5 cm followed by sonication sequentially in 95% ethanol and DI water for 15 min. Plasma treatment was performed in a chamber equipped with radio frequency (RF) generator plasma [35] consisted of three main parts: (i) a reaction chamber, (ii) a RF generator, and (iii) a vacuum system. The chamber size is 30 cm × 30 cm × 30 cm and the distance between electrodes and the samples was fixed at 7 cm. The electrode employed is a shower-type cathode with diameter of 15 cm. The PCL membrane was treated by O_2 plasma under the flowrate of 20 sccm, the applied power of 100 W, and the total pressure of 100 mTorr for 60 s.

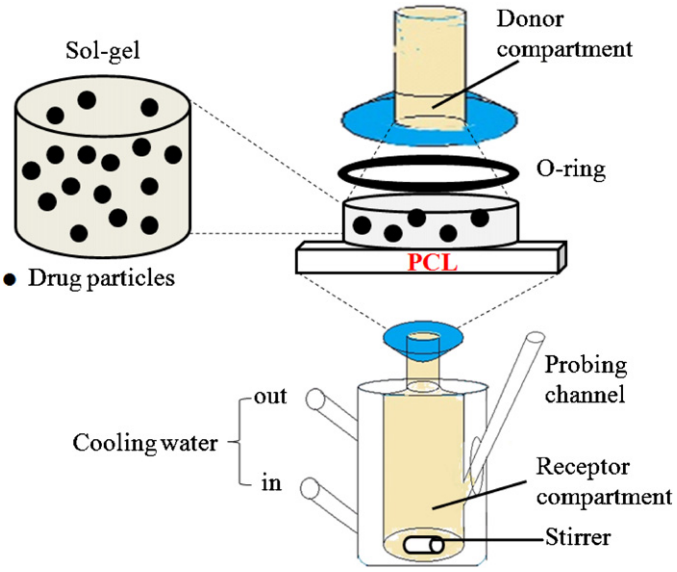

Fig. 1. Schematic diagram for the modified Franz diffusion cell.

2.4. Drug release analyses by using Franz diffusion cells

In vitro drug release experiments were carried out by using a modified Franz diffusion cell [32,33] depicted in Fig. 1. PCL membranes (with and without plasma treatment) were clamped between donor and receptor compartments where the surface area between the two compartments was 1.767 cm^2. Highly porous side of PCL membrane was placed facing the receptor compartment, while the less porous one faced donor compartment. The donor part contained 1 mg/mL model drug (AgSD or ketoprofen) in sol–gel, the receptor included 24 mL of PBS with pH of 7.4. The drug release experiments, using the Franz diffusion cells, were performed under stirring and with a constant temperature of 37 °C. The released content, 200 μL, was taken and measured at fixed time intervals from the receptor part while another 200 μL PBS was immediately added back into the receptor part. The concentration of drug was monitored by using enzyme-linked immunosorbent assay (ELISA, iMark Absorbance Reader, BioRad) at λ_{max} of 310 and 300 nm for ketoprofen, and AgSD, respectively. Typical UV–vis peaks for the ketoprofen and AgSD is shown in Fig. S1 (in Supplementary Information). The measurements of drug concentration which varied due to the sample uptake and refill of PBS in the Franz diffusion cell were corrected by using the calculation provided by Klimundová et al. [36]:

$$C_{n,\text{corrected}} = C_{n,\text{measured}} + \left(\frac{V_{\text{drawn}}}{V_{\text{receptor}}}\right) \cdot C_{n-1,\text{measured}} \quad (1)$$

where $C_{n,\text{measured}}$ = measured concentration of n-sample or $(n-1)$-sample; V_{receptor} = volume of receptor; and V_{draw} = volume of liquid drawn out.

2.5. Surface characterizations

To determine the wettability of PCL membranes, the sessile drop was added on the surface of samples and was analyzed by using contact angle goniometer (Sindatek 100SB, Taiwan). The water contact angle (WCA) was calculated by using Magic Droplet® software. At least five droplets were used to determine the average of WCA. The morphology of the membranes was observed by using scanning electron microscope (SEM, JEOL JSM-6300). The