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Photocuring of stimulus responsive membranes for controlled-release of drugs having different molecular weights

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Abstract

Intelligent drug delivery membranes were prepared by photocuring poly(acrylic acid) coatings onto poly(2-hydroxyethyl methacrylate) membranes each with model drugs of different molecular weights being incorporated. pH-responsive release behaviours of the model drugs which included sodium salicylate, nicotinamide, nicotinic acid, methylene blue, brilliant green and crystal violet were investigated. Only the membrane with methylene blue incorporated showed a clear pH-responsive release and other drug-incorporated membranes showed no intelligent behaviour. These phenomena were explained in terms of the difference in diffusivity of drugs through polymer matrices of the membranes attributable to the difference in the molecular weights of drugs.

Keywords: Photopolymerisation; Biomembranes; pH-responsive coating; pH-responsive release; Molecular weight of drug; Matrix diffusion

1. Introduction

Studies on the environmentally responsive permeation and controlled release of drugs using stimulus sensitive hydrogels have been extensively conducted in the past years by researchers all over the world (Tanaka et al., 1982; Kaetsu et al., 1992; Rosiak and Yoshii, 1999; Carenza et al., 2000). These stimulus sensitive hydrogels, which have been employed for intelligent control of drug delivery have special properties of either being pH, electro- or thermo-responsive. The hydrogels that exhibit pH and electro-sensitivity are comprised of polyelectrolytes and polyampholytes, while the thermo-responsive hydrogels have special chemical structures of hydrophilic–hydrophobic balance and exhibit a lower critical solution temperature (LCST).

In recent years, Kaetsu and co-workers have developed a technique for the preparation of "intelligent" controlled-release membranes by means of free-radical induced photopolymerization (Kaetsu et al., 2001). It was demonstrated that drug-incorporated poly(2-hydroxyethyl methacrylate) (PHEMA) membranes coated with pH-responsive polymeric hydrogels such as poly (acrylic acid) (PAAc) promoted the drug release in acidic medium and retarded the release in alkaline medium.

PAAc coating being acidic in nature is expected to swell in alkaline medium. This is attributed to the repulsion of anionic charges of carboxylate ions, which are formed by the deprotonation of carboxylic acid

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functional groups present in the PAAc polymer chains when they undergo acid–base neutralisation reaction. It is expected that repulsion between the resultant anion charges would lead to an extended conformation in the polymeric chains. Thus PAAc coating expands or swells under alkaline conditions resulting in the decrease in pore sizes within the polymeric matrix. However, when the expanded coating is subsequently placed in an acidic medium, it is expected to shrink due to the diminishing anion repulsion effects as the $-COO^-$ groups in the polymeric chains are being protonated by H^+ ions present in the aqueous acidic environment. Thus the on–off switching mechanism is attributable to the response of the pH stimulus sensitive coating to the signal imparted according to the pH in the environment. Such responses will contribute to certain trends in controlled release of drugs.

Recently, Nakayama et al. (2003a) synthesised and investigated UV cured biomembranes coated with pH and thermal responsive polymer coatings such as PAAc and poly(*N*-isopropyl acrylamide) [poly(NIPAAm)], respectively on the drug-incorporated base membrane for nicotine release in relation to anti-smoking effect. They also used membranes with poly(NIPAAm) coatings for the controlled release of fragrances such as orange, bergamot and lemon fragrances (Nakayama et al., 2003b). However, these research works were carried out using only limited model drugs as mentioned. Therefore, further studies using different kinds of drugs for the intelligent controlled release would be necessary.

From this point of view, the current authors studied the pH-responsive release of various model drugs with different molecular weights incorporated in a porous membrane comprised of PHEMA, which was coated with PAAc. The bi-layer membrane thus synthesised had an interpenetrating polymer network structure, as AAc monomer was introduced onto the already formed PHEMA and subsequently polymerised. The effects of the molecular weight of drugs on the intelligent release from PHEMA membrane through PAAc coating were evaluated.

2. Experimentals

2.1. Reagents and materials

The monomers, acrylic acid and 2-hydroxyethyl methacrylate, as well as model drugs, brilliant green and crystal violet were obtained from Wako Pure Chemicals, Japan. Other model drugs, methylene blue, nicotinamide and nicotinic acid were from Sigma, and sodium salicylate was obtained from Chameleon Chemical Reagent, Osaka, Japan. The photoinitiator, Irgacure 819 was from Ciba and the crosslinking agents, polyethylene glycol dimethacrylate #400 (9G) and tetraethylene glycol dimethacrylate #200 (4G) were procured from Shin Nakamura Chemical Co. Ltd. All these reagents, which were of high-purity grade were used as received.

2.2. Synthesis of drug-incorporated membranes

Drug-incorporated membranes were prepared according to the method described in the previous paper by Nakayama et al. (2003a). Solutions comprising of appropriate model drug:HEMA:9G:Irgacure 819 in the ratio of 2.0: 69.0: 28.7: 0.3 (% w/w), respectively, were prepared. The solutions were each casted into a plane space of 2.0–2.5 mm sandwiched between two poly (ethylene terephthalate) films and further reinforced with two glass plates. This system was irradiated with a UV source to a total dose of 4.8×10^2 J (intensity of 0.66×10^4 μW/cm^2) from a high-pressure mercury lamp (400 W).

2.3. Coating and curing of PHEMA membrane with PAAc coating

A solution comprised of AAc: 4G: Irgacure 819 in the ratio of 49.95: 49.95: 0.1 (% w/w) was prepared to be coated onto drug-incorporated membranes. 4G being more hydrophobic than 9G was the crosslinker used in this formulation so as to reduce the rate of coating being swollen too rapidly in an aqueous environment. Firstly, one surface of each membrane was coated with AAc solution and then inserted into a polyethylene bag, filled with N_2 gas and sealed before being subjected to UV irradiation to a total dose of 1.7×10^2 J from the high-pressure mercury lamp. The reverse side of the membrane was coated in the similar manner. The thickness of coatings affects the rate of drug release though not on the release trends. The thickness of each membrane was measured before and after the coating on both surfaces of the membrane and the coating thickness on one surface of the membrane in each system prepared was within the range of 0.06–0.3 mm. These measurements were taken at the diagonal corners (A and C) and the centre (B) of each membrane sample (as stated in captions for Figs. 2–6). Fig. 1 depicts the schematic diagram for the preparation process of the intelligent membrane. The basic structure of a photo-cured drug-incorporated membrane is shown in the diagram.

2.4. Intelligent release test and analysis

The membrane coated with a pH-responsive polymer, PAAc was initially immersed in a pH 10 solution for 1 h to allow the coating to expand and at the same time to induce the release of drug into the aqueous medium. The coated membrane was then tested for drug release at ambient temperature by immersing it alternately in