The Electro-Responsive Drug Delivery From Salicylic Acid- Loaded Polyacrylamide Hydrogels

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Acrylic elastomers, SAR, SBR and SIS thin sheets were fabricated through solvent casting and electrorheological properties were measured and tested towards electroactive applications such as artificial muscle and/or MEMS devices. Experiments were carried under the oscillatory shear mode with applied electric field strength varying from 0 to 2 kV/mm. The effect of temperature on the storage and loss modulus (G' and G"), storage modulus sensitivity ($\Delta G'/G'_0$), and dielectric permittivity of acrylic elastomers (AR70, AR71, and AR72), SAR, SBR and SIS D1112P were studied between 300-370 K. AR71 has the highest dielectric permittivity (ε') of 55.98 pF/m, whereas SIS D1112P has the lowest dielectric permittivity of about 24.28 pF/m. From our data, we can classify the elastomers into two types. Acrylic group has positive storage modulus sensitivity with increasing temperature and dielectric constant, and the styrene copolymer group has negative storage modulus sensitivity.

1. Introduction

A number of intelligent drug delivery devices have been proposed to deliver the drug for efficient therapy. Intelligent drug delivery systems (DDS) are one expected results, demonstrating ability to sense external environmental changes, to judge the degree of external signal, and to release appropriate amounts of drug. Intelligent DDS may be received using stimuli-responsive polymeric hydrogels which can alter their structure and physical properties in response to external stimuli such as electric fields, pH and temperature.

Hydrogels have attracted considerable attention as an excellent candidate for intelligent DDS due to their swelling behavior, adhesiveness and biocompatibility (Alvarez-Figueroa *et al*., 2001, p. 57 and Baljit *et al*., 2007, p. 559). An electric field stimulus is the most attractive because it allows precise control. There is already a large body of literature on the use of electric currents in vivo, in from of iontophoresis and electroporation (Murdan *et al*., p. 1). Banga *et al.,* 1993 demonstrated the feasibility of using electric current to control and predict release rates of vasopressin from polyacrylamide hydrogel; they suggested that the release of drug from a hydrogel matrix under action of electric field strength was more than the release in the absence of electric field. The same behavior was observed for the releases of insulin, protein molecule, from polyacrylamide hydrogels.

Therefore, this study is an attempt to prepare polyacrylamide hydrogel by using N, N'-MBA as the crosslinker agent and ammonium peroxodisulfate as the initiator and thereafter utilization of these hydrogels to study the release dynamic of a model drug, salicylic acid, from drug loaded samples. The data obtained were analyzed to describe the effects of electric field and crosslink ratio on the release mechanism and diffusion coefficient of the model drug from these polyacrylamide hydrogels.

2. Methodology

2.1 Materials

Salicylic acid (AR grade, Fluka) was used as model drug. Acrylamide ,AAm (AR grade, Fluka), N,N' methylenebisacrylamide, MBA (AR grade, Fluka), tetramethylenediamine, TEMED (AR grade, Fisher Scientific) and ammonium peroxodisulfate (AR grade, Fluka) were used as monomer, crosslinker, catalyst and initiator, respectively. Sodium acetate and acetic acid (AR grade, aldrich) were used to prepare buffer solution (pH 5.5).

2.2 Preparation of salicylic acid loaded- polyacrylamide hydrogel (salicylic acid loaded- pAAm)

Table 1 shows the compositions of 6 physically different polyacrylamide hydrogels prepared by following the approach describe by Wallace *et al.*. Different amounts of both acrylamide (AAm) and N,N' methylenebisacrylamide (MBA) were added to salicylic acid solution, 0.0125 M. After solutions being degassed with N_2 during 10 min, tetramethylenediamine (TEMED) and ammonium peroxodisulfate were added under stirring. Before gelification (typically after 10 min of mixing the reagents at room temperature), 8 ml of pre-gel solution was cast in the petri-dish. After gelification, polyacrylamide hydrogel was cut into spherical shape (diameter = 18 mm, thickness = 0.5 mm)

2.3 Preparation of buffer solution

Buffer solution of pH 5.5 was prepared by taking 15 mL of glacial acetic acid and 150 g of sodium acetate in volumetric flask to make volume 1,000 mL.

2.4 Characterizations

Scanning electron micro graphs were taken with a scanning electron microscope (JEOL, JSM-5200-2A) using an acceleration voltage of 15 kV and a magnification of 1500. Frontal images of hydrogels with and without electric field were obtained in high vacuum mode. Samples were prepared by frozen swollen hydrogel with and without electric filed in liquid nitrogen and liofilization in the microscope vacuum chamber.

2.5 In vitro drug release from polyacrylamide hydrogel

The pig skin (thickness ~ 1-1.5 mm) was placed on the modified franz diffusion cell and the area available for permeation was 3.14 cm^2, the skin was equilibrated for 2 h with acetate buffer (pH 5.5) in the receptor chamber and was magnetically stirred throughout

the experiment (48 h) at thermostatically maintained temperature (37 ± 2 ^{0}C). The amount of drug release was measured as functions of crosslinking ratio (mol $_{AAm}$: mol $_{MBA}$; 0.005, 0.01, 0.02, 0.035, 0.065) and electric field strength (0-10 V) for 48 hr. And the amount of drug release was determined using UV-VIS spectrometer (Lambda 10).

3. Results and Discussions

3.1 In vitro drug release from polyacrylamide hydrogel

3.1.1 Effect of cross-linking ratio

The amounts of salicylic acid release versus square root of time plots for various cross-linking ratios in the absence of electric field are shown in figure 2. The amount of salicylic acid release is quite and large with a sample with a lower amount of cross-linking ratio. The release becomes slower with a sample with a higher cross-linking ratio. Thus, the amount of salicylic acid release is slower and lower at a higher amount of cross-linking ratio because the hydrogel is more rigid due to the contraction of the pore as shown in SEM micrographs in figure 1. This would decrease the swelling, which will further decrease the amount release of salicylic acid through the hydrogel.

3.1.2 Drug release kinetics

Drug release kinetics was analyzed by plotting the amount of drug release data versus square root of time and by fitting these data to the Higuchi's equation

$$Q = 2C_0 (Dt/\pi)^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area; C_0 is the initial drug concentration in the gel; and D is the diffusion coefficient of a diffusant. Using the slope of plot, we have estimated the diffusion coefficient for all crosslinking ratios. Figure 4 shows the diffusion coefficient of polyacrylamide hydrogels versus crosslinking ratio at electric field strengths of 0 and 0.1 V at 37 ^{0}C. From these data, we can finally conclude that the diffusion coefficient decreases with increasing crosslink ratio due to the larger pore size. When the electric field is applied, the diffusion coefficient increases due to the electrostatic force driving the polar drug, salicylic acid (Banga *et al.,* 1993, p. 697). At electric field strength of 0.1 V, the pore size of polyacrylamide hydrogel is expanded as shown in SEM micrographs (figure 3).

4. References

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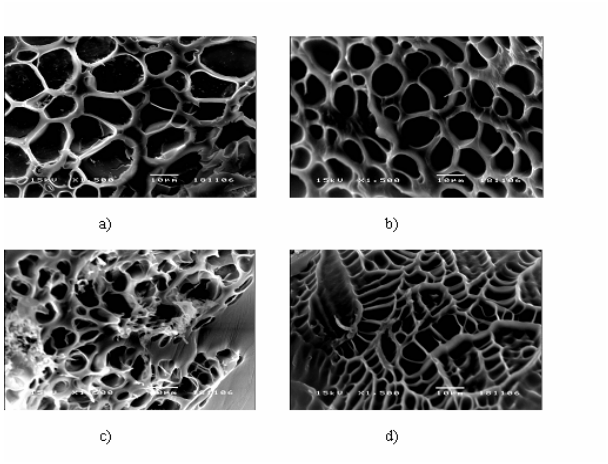


Fig.1 The morphology of Polyacrylamide hydrogel after swelling:
a) PAAM_0.005; b) PAAM_0.01; c) PAAM_0.035; and d) PAAM_ 0.065 at magnification of 1500.

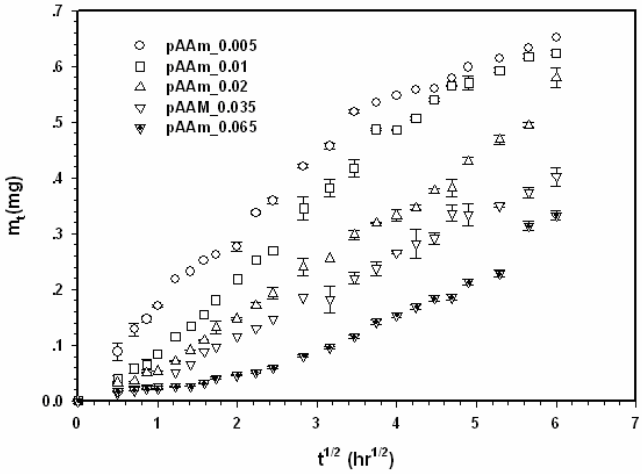
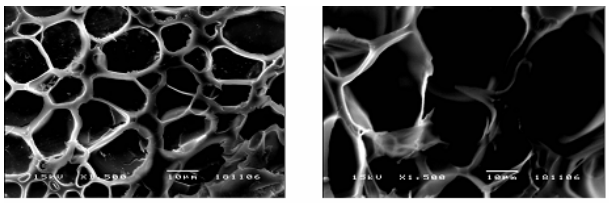


Fig. 2 Amount of salicylic acid release from salicylic acid loaded polyacrylamide hydrogel at time t vs. $t^{1/2}$ at various crosslink ratios, E = 0 V, 37^{o}C.



a) b)

Fig.3 The morphology of Polyacrylamide hydrogel (PAAM_0.005) after swelling under electric field strength of: a) 0 V and b) 0.1 V at magnification of 1500.

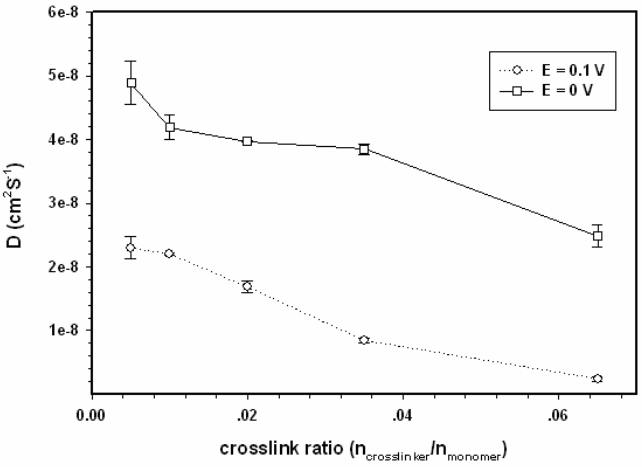


Fig.4 Diffusion coefficient of polyacrylamide hydrogels vs. crosslink ratios at electric field strength of 0 and 0.1 V, 37 ^{o}C.