Electrically controlled aloin and benzoic acid release from polyacrylamide hydrogel: effect of drug size and electric field strength

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***Abstract*— The effects of hydrogel mesh size, drug ionic strength, and electric field strength on controlled drug delivery phenomena using drug-loaded polyacrylamide hydrogels (drug-loaded PAAM) prepared at various crosslinking ratios. The interested model drugs are aloin and benzoic acid which have difference size and ionic strength. In passive release (without external electric field stength), the amountof model drug released from crosslinked PAAM hydrogel increase with increasing hydrogel pore size (decreasing crosslinking ratio) and electric field strength. When the external electric field was applied, PAAM hydrogel pores were expanded and ionthophoresis of anionic drug was occured. As higher electric field strength, higher electro-repulsion force drive anionic drug through PAAM hydrogel and higher electroporation generated. The amount of benzoic acid released is higher than aloin release due to the smaller size and stronger ionic strength. The kinetic of drug release from PAAM hydrogels were investigated by calculation of diffusion coefficient, D. D of benzoic acid released is higher than D of aloin released at given crosslinking ratio and electric field strength. Thus, the drug size and the electric field could be used in combination to regulate the amount of release drug to a desired level, to control the release amount and rate.**

1. Introduction

Transdermal drug delivery, TDD is very interested drug delivery method trough skin to blood circulation. TDD has many advantages over oral and injection method but passive TDD has limitation from epidermis barrier. Thus iontophoresis TDD, which enhances drug delivery across epidermis barrier with assistance of an external electric field, becomes important method in deliver drug. Hydrogel is a major role material for TDD [1-2]. Hydrogels, consisting of tri-dimensional structures formed by crosslinking hydrophilic polymeric chains, possess the ability to swell in solution in response to the chemical nature of the media, the pH, the ionic strength, the electric field, and temperature.

In the past decade, many researchers already known the hydrogel pore size and electric field strength can control the drug level and drug delivery kinetic [3-4]. But the drug size and the intensity of interaction between drug and hydrogel are not well understood. Thus in this work, we will investigate effect of drug size and intensity of interaction between drug and hydrogel on drug delivery phenomena. Benzoic acid and aloin were selected as the model drug. Polyacrylamide hydrogel was selected as the model hydrogel.

2. Methodology

2.1 Materials

Aloin (AR grade, Fluka) and benzoic acid (AR grade, Fluka) were used as the model drug. Acrylamide (AAM) (AR grade, Fluka, China); N,N′ methylenebisacrylamide (N,N´-MBA) (AR grade, Fluka); tetramethylenediamine (TEMED) (AR grade, Fisher Scientific); and ammonium peroxodisulfate (AR grade, Fluka) were used as the monomer, crosslinker, catalyst, and initiator, respectively. Sodium acetate (AR grade, Ajax Chemicals) and glacial acetic acid (AR grade, Mallinckrodt Chamicals) were used in this study without further purification.

2.2 Preparation of drug-loaded polyacrylamide hydrogel (drug/PAAM)

The 0.2 %w/w drug-loaded PAAM hydrogels (based on the weight of the acrylamide monomer) were prepared by the free-radical polymerization of 2.32 g of acrylamide in an aqueous solution of drug (Aloin and Benzoic acid) with N, N′ methylenebisacrylamide (MBA) as crosslinker [3]. Ammonium persulfate and tetramethylenediamine (TEMED) were used as the initiator and the accelerator. To study the effect of crosslinking ratio on the release of drug from drug/PAAM hydrogels,

gels at various crosslink ratios (mol MBA: mol AAM; 0.001, 0.002, 0.005, 0.010, 0.016, 0.024; PAAM_01, PAAM_02, PAAM_03, PAAM_04, PAAM_05, PAAM_06, respectively) were prepared at various amounts of N, N ′ methylenebisacrylamide (MBA).

2.3 Drug-loaded polyacrylamide hydrogel (drug/PAAM) charcaterization

DSC thermograms of the drug (Aloin and Benzoic acid), the PAAM hydrogel, and the drug-loaded PAAM hydrogel were recorded to determine their thermal behavior. The 2-4 mg sample was accurately weighed in an aluminum pan with a sealed cover. The measurements were performed under N2 atmosphere over 30 – 400 ˚C at heating rate of 10 ˚C/min.

2.4. Release of drug from drug/PAAM Hydrogel Experiments

Transdermal diffusion through a hairless pigskin was carried out in order to study the release characteristics of the drug from a drug/PAAM hydrogel. A hairless pigskin (thickness ~ 1-1.5 mm) was placed on top of the acetate buffer solution on a custom built modified Franz diffusion cell. The pigskin was allowed to come into equilibrium contact with the acetate buffer in the receptor chamber; the buffer was magnetically stirred throughout the experiment period (24 h) at a thermostatically maintained temperature (37 ± 2 ˚C). The drug/PAAM hydrogel with a particular crosslinking ratio was placed between the cap and the pigskin, which was mounted onto the receptor compartment. The buffer solution, 0.3 ml was withdrawn and an equal amount of fresh buffer solution was added to the cell, every 15 minutes during the first hour. The amount of the drug in the withdrawn solution samples was determined using a UV spectrophotometer [5].

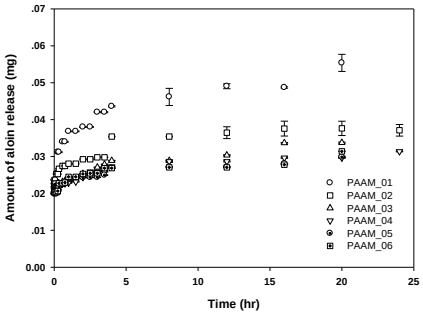
3. Results and Discussion

3.1 Drug-loaded polyacrylamide hydrogel (drug/PAAM) charcaterization

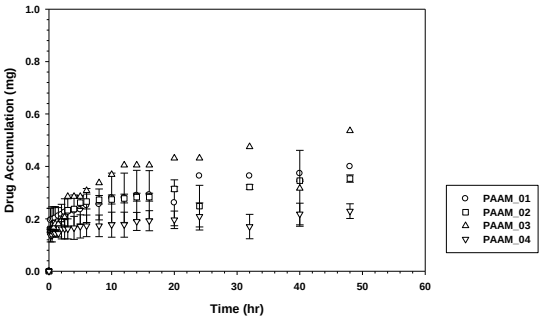
DSC thermograms of, drug-loaded PAAM hydrogel, and PAAM hydrogel were measured to investigate the interaction between drug (aloin and benzoic acid) and the polyacrylamide matrix. The melting temperature (Tm) of PAAM is 219 ˚C, consistent with a previous report [6]. However, the Tm of PAAM in drug-loaded PAAM occurs at 241 and 243 ^{o}C for aloin and benzoic acid, respectively. This evident might be concluded that aloin possibly interacts with the PAAM hydrogel through hydrogen bonding between the hydroxyl groups of the aloin and the amine groups of the PAAM hydrogel. Benzoic acid also interacts with PAAM hydrogel through hydrogen bonding. From the structure og aloin and benzoic acid, benzoic acid might have higher strength of interaction with hydrogel.

3.2 Release characteristic

The amount of drug released through the pig skin was reported as the amount of aloin and benzoic acid released from PAAM as shown in Fig.1 (a) and (b), respectively. In the passive release characteristic (E = O V), the amounts of aloin and benzoic acid released from PAAM were noticeably high during the first 2-4 hours and reached the equilibrium value afterward. Evidently, the amount of drug released from PAAM through the pig skin was greater at a given time for samples with a lower crosslinking ratio [17]. A lower crosslinking ratio represents a larger hydrogel mesh size, suggesting that the deliver pathway is larger and thereby a greater quantity of released drug is obtained [18].



(a)



(b)

Fig.1. Amounts of (a) aloin and (b) Benzoic acid released from aloin/PAAM hydrogel at time t vs. t (hr) at various crosslinking ratios, E = 0 V, pH 5.5, and at 37˚C.

Fig. (2) shows the amounts of aloin released from aloin-loaded PAAM in relation to time at various electric field strengths, 0–0.1 V. Each sample was attached to the negatively charged electrode (cathode). From Fig.(2), it is evident that the amount of aloin released from aloin/PAAM was greater at a higher electric field strength due to three driving forces: electrostatic force, the modified pathway of pig skin, and expansion of PAAM hydrogel. As the electric field was applied, the electrons pushed the anionic out and generated small pathways in the pig skin. Thus, the higher the electric field strength, the greater the amount of aloin released. The third driving force, i.e. expansion of PAAM hydrogel, was the direct result of the expansion of the PAAM hydrogel pore size following the application of the electric field [4,7].

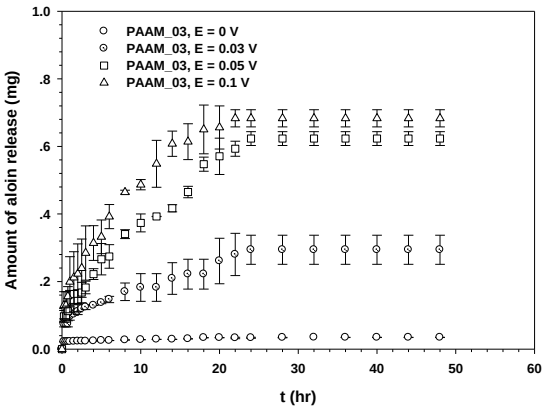


Fig. 2 Amounts of aloin released from aloin/PAAM hydrogel (PAAM_03) at time t vs. t (hr) at various electric field strengths, pH 5.5, and at 37 °C.

The apparent diffusion coefficients, D_{app} of drug diffuse from drug loaded PAAM were determined by Higushi's equation;

$$Q = 2C_0(D_{app}t/\pi)^{1/2} \qquad (1)$$

where Q is the amount of drug released per unit area, C_0 is the initial drug concentration in the gel, and D_{app} is the apparent diffusion coefficients diffusion coefficient of a diffusant [7]. We may note D_{app} obtained from Eqs. (1) are valid over an initial period of time and based on the Fick's laws.

The effect of pore size and electric field on D_{app} is shown in Fig.3. The D_{app} also

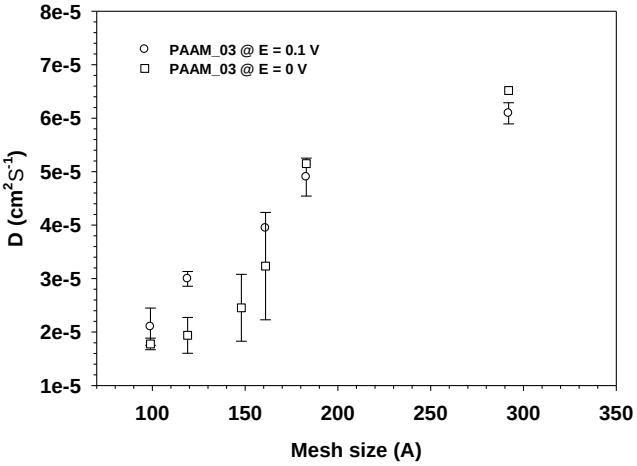


Fig. 3 The diffusion coefficient, D_{app} of Aloin from Aloin/ PAAM hydrogel (E = 0 and 0.1 V) vs. Mesh size at pH 5.5, and at 37 °C.

increases with increasing hydrogel pore size and electric field. For larger pore size of hydrogel system, aloin can easily diffuse out than smaller pore size hydrogel system. Thus, the amount of aloin released and D_{app} can be controlled by controlling the hydrogel pore size electric field [8-14].

4. Conclusion

To study the effect of drug size, interaction between drug and hysrogel and electric field strength, the drug-loaded PAAM (aloin and benzoic acid) were prepared to use as the transdermal drug delivery patch. The drug-loaded PAAM at various crosslinking ratios were prepared to study the effects of pore size on the release profile both with and without applying electric field strengths (0-0.1 V). The amount of released aloin and diffusion coefficient, D, increased with increasing hydrogel mesh size and electric field strength. As the electric field was applied (0-0.1 V), the amount of released aloin increased with increasing electric field strength which drove ionic drug through polyacrylamide hydrogel with increase in electrostatic force, modified the pathway of pig skin, and expanded PAAM hydrogel pore size.

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