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Controlled Benzoic Release from Crosslinked Polyacrylamide Hydrogels: Effects of Mesh Size, Electric Field Strength

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ABSTRACT

The effect of crosslink in g ratio and electric field strength on the release characteristic of acid drug from poly acryl amide hydro gel was investigated. Benzoic acid and poly acryl amide hydro gel were selected as the model drug and hydro gel, respectively. The release characteristic of benzoic acid in with and without applying electric field system showed the similar results, the amount of drug released gradually increase with increasing released time and reached the equilibrium value at 10 hr. The amount of drug released increase with increasing mesh size because the drug easily moves out from the hydro gel at the larger mesh size. The amount and rate of drug release increase when the electric field strength of 0.5 V is applied. There are two mechanisms which can describe these results; the electrostatic force between electrode and ionic drug and micro pathway in pigskin. As the electric field is applied, electron from cathode electrode pushes the ionic drug by electrostatic force and electric field can generate the micro pathway in pigskin. The diffusion coefficient, D of the drug released from poly acryl amide hydro gel at various crosslink in g ratios at E= 0 and 0.5 V were calculated. D also increases with increasing hydro gel mesh size and electric field strength.

Key words: Benzoic acid, Controlled Drug delivery, Iontophoresis, Diffusion coefficient, Poly acryl amide

INTRODUCTION

Recently , the increasing interest in trans dermal drug delivery system, TDD due to many advantages over conventional delivery method (oral route and injection): effective systemic delivery, high patent compliance, constant rate release and easily terminated (patch removal after used) [1]. There are many TDD patch products in market in passive form which has limitation from epidermis barrier; it is hence responsible for the poor permeability of skin. To overcome permeability of skin in passive TDD, micro needle, active interaction, stratum cornea modification, stratum cornea bypass and electrically assisted method is required. Ion to pho res is is one of popular electrically assisted method because ease to controlled. Thus ion to pho res is TDD, which enhances drug delivery across epidermis barrier with assistance of an external electric field, becomes important method in deliver drug. Hydro gel is a major role material for TDD [1-2]. Hydro gels, consisting of tri-dimensional structures formed by crosslink in g hydrophilic polymeric chains, able to swell in water in response to the chemical nature of the media, the pH, the ionic strength, the electric field, and temperature. Benzoic acid is used for the treatment of fungal skin diseases such as tine, ringworm, and athlete's foot[2]. This research work l fabricated the benzoic acid TDD patch from poly acryl amide hydrogen. The effect of external electric field, hydro gel mesh size and intensity of interaction between drug and hydro gel on drug delivery phenomena.

Materials And Methods

2.1 Materials:

Benzoic acid (AR grade, Fluka) were used as the model drug. Acryl amide (AAM) (AR grade, Fluka, China); N,N′ methylenebis acryl amide (N,N´-MBA) (AR grade, Fluka); tetramethylenedia mine (TEMED) (AR grade, Fisher Scientific); and ammonium peroxodisulfate (AR grade, Fluka) were used as the monomer, cross linker, catalyst, and initiator, respectively. Sodium acetate (AR grade, Ajax Chemicals) and glacial acetic acid (AR grade, Mallinckrodt Chemicals) were used in this study without further purification.

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2.2 Preparation of benzoic-loaded poly acryl amide hydrogen (benzoic acid/PAAM):

The 0.2 %w/w drug-loaded PAAM hydro gels (based on the weight of the acryl amide monomer) were prepared by the free-radical polymerization of 2.32 g of acryl amide in an aqueous solution of benzoic acid drug with N,′ Nmethylenebisacryl amide (MBA) as cross linker [3]. Ammonium per sulfate and tetramet hylenedi amine (TEMED) were used as the initiator and the accelerator. To study the effect of crosslinking ratio on the release of drug from drug/PAAM hydro gels, gels at various crosslink ratios (gMBA: gAAM; 0.005, 0.035, 0.080 and 0.10; PAAM_01, PAAM_02, PAAM_03, PAAM_04, respectively) were prepared at various amounts of N, N′ methylenebisacrylamide (MBA).

2.3 Swelling and mesh size of PAAM hydrogen:

To determine the % swelling of the PAAM hydro gels at various crosslink ratios, they were immersed in an acetate buffer, pH 5.5, at 37 ˚C. After 5 days the swollen PAAM hydro gels were removed, gently wiped to clean off the surface water, and then re-weighed. The % swelling and the % weight loss were calculated using the following equations [1]:

$$\text{Degree of swelling (\%)} = \frac{M-M_d}{M_d} x100 \quad (1)$$

where M is the weight of a swollen sample, M_d is the weight of swollen sample after drying in vacuum oven, and M_i is the initial weight of the sample [1]. Hydrogen mesh sizes were calculate from equation 2:

$$\xi = v_{2,s}^{-\frac{1}{3}}\left[C_n\left(\frac{2M_c}{M_r}\right)\right]^{1/2} l \quad (2)$$

where ξ is hydrogen mesh size, M_c is molecular weight between crosslink, M_n is monomer molecular weight, C_n is Flory characteristic ratio of poly acryl amide hydrogen, 8.8, $v_{2,s}$ is swollen polymervolume fraction and l is carbon-carbon length, 1.54 ÅAll reported data were average values taken from repeated measurements using five specimens.

2.4Benzoic acid-loaded poly acryl amide hydrogen (benzoic acid/PAAM) characterization:

DSC thermo grams of the benzoic acid, the PAAM hydrogel, and the benzoic acid-loaded PAAM hydrogen 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 N_2 atmosphere over 30 – 400 ˚C at heating rate of 10 ˚C/min.

2.5 Release of drug from benzoic acid/PAAM Hydrogen Experiments:

Transversal diffusion through a hairless pigskin was carried out in order to study the release characteristics of the drug from a benzoic acid/PAAM hydrogen. A 1-1.5 mm hairless pigskin was placed on top of the acetate buffer solution on a modified Franz diffusion cell. The pigskin was allowed to come into equilibrium contact with the buffer solution pH of 5.5 in the receptor chamber; the buffer was magnetically stirred throughout the experiment period (48h) at a thermostatically maintained temperature (37 ± 3˚C). The benzoic acid/PAAM hydrogen with a particular cross linking ratio was placed between the cap and the pigskin, which was mounted onto the receptor compartment. To apply the external electric field, the cathode copper electrode was place on benzoic acid/PAAM hydrogen and anode co 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].

Results and Discussion

3.1Swelling and mesh size of PAAM hydrogen:

In this present work, the degree of swelling is related to the amount of gel required to achieve a suitable. As expected intuitively, the degree of swelling is inversely proportional to the degree of cross linking as shown in Fig. 1. These results are consistent with theoretical predictions which describe the swelling of gel as a function of the degree of cross linking [2]. The calculated mesh sizes are 64 ±17.54, 31±0.38, 23±0.45 and 11±0.25 Å for PAAM_01, PAAM_02, PAAM_03 and PAAM_04, respectively.

3.2 Benzoic acid-loaded poly acryl amide hydrogen (drug/PAAM) characterization:

DSC thermo grams of, Benzoic acid-loaded PAAM hydrogen, and PAAM hydrogen were measured to investigate the interaction between benzoic acid and the poly acryl amide matrix. The melting temperature (T_m) of PAAM is 2033 However, the Tm of PAAM from benzoic acid-loaded PAAM occurs at 272 ˚C, suggesting that benzoic acid possibly interacts with the PAAM hydrogen through hydrogen bonding between the hydroxyl groups of the aloe in and the amine groups of the PAAM hydrogen corresponding to FTIR results. 3.2 Release characteristic

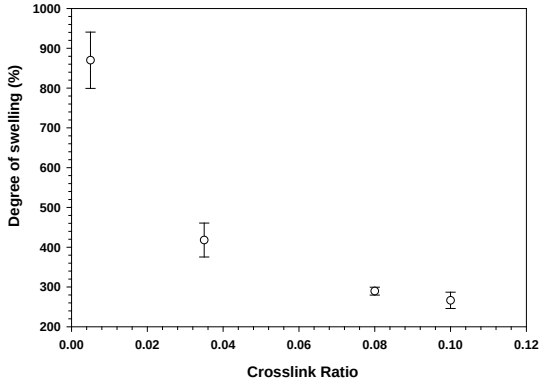

Fig. 1: %swelling of crosslink poly acryl amide hydrogen at various cross linking ratio

The amount of drug released through the pig skin was reported as the amount of benzoic acid released from PAAM as shown in Fig.2. In the passive release characteristic (E = O V), the amounts of benzoic acid released from PAAM were increase at first 2-4 hours and reached the equilibrium amount afterward. Evidently, the amount of drug released from PAAM through the pig skin increase with increasing hydrogen mesh size [6]. A lower cross linking ratio represents a larger hydrogen mesh size, suggesting that the deliver pathway is larger and thereby a greater quantity of released drug is obtained [6].

Each sample was attached to the negatively charged electrode (cathode). From Fig.3, it is evident that the amount of benzoic acid released from 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 hydrogen. 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 benzoic acid released. The third driving force, i.e. expansion of PAAM hydrogen, was the direct result of the expansion of the PAAM hydrogen pore size following the application of the electric field [7].

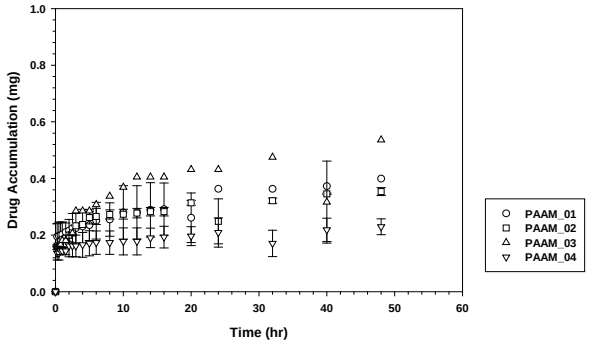

Fig. 2: Amounts of benzoic acid released from PAAM hydrogen at time t vs. t (hr) at various cross linking ratios, E = 0 V, pH 5.5, and at 37˚C.

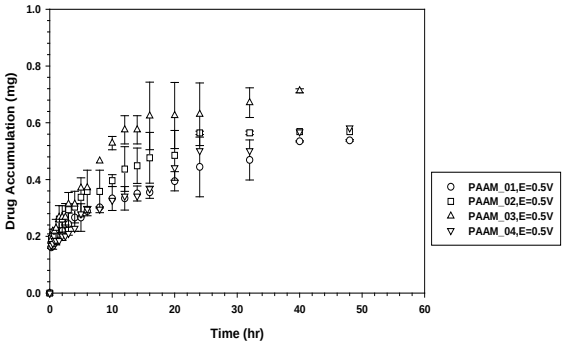

Fig. 3: Amounts of benzoic acid released from PAAM hydrogenate time t vs. t (hr) at electric field strengths of 0.5 V, pH 5.5, and at 37˚C.

The apparent diffusion coefficients, *D* of drug diffuse from drug loaded PAAM were determined by Higushi's equation;

$$Q = 2C_0(Dt/\square)^{1/2} \quad (3)$$

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 apparent diffusion coefficients diffusion coefficient of a diffusing [3,7]. We may note D obtained from Eqs. (4) are valid over an initial period (before 10 h) of time and based on the Flick's laws.

The effect of pore size and electric field on D is shown in Fig.4. The D also increases with increasing hydrogen pore size and electric field. For larger pore size of hydrogen system, benzoic acid can easily diffuse out than smaller pore size hydrogen system. Thus, the amount of benzoic acid released and D can be controlled by controlling the hydrogen pore size and electric field [7].

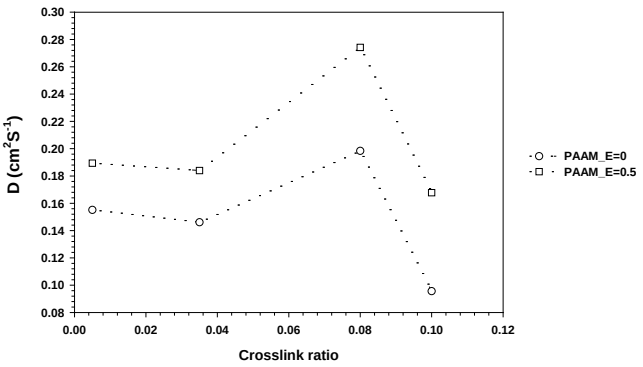

Fig. 4: The diffusion coefficient, D of benzoic acid from PAAM hydrogen (E = 0 and 0.5V) vs. cross linking ratio at pH 5.5, and at 37 ˚C.

Conclusion:

To study the effect of interaction between drug and hydrogen and external electric field, the benzoic acid-loaded PAAM were prepared to use as the electro-transversal drug delivery patch. The benzoic acid-loaded PAAM at various cross linking ratios were prepared to study the effects of pore size on the release profile both with and without applying electric field strengths (0 and0.5V). The amount of released benzoic acid and diffusion coefficient, D, increased with increasing hydrogen mesh size and electric field strength. As the electric field was applied, the amount of released benzoic acid increased under apply electric field which push ionic drug through poly acryl amide hydrogen via electrostatic force, modified the pig skin pathway , and expanded PAAM hydrogen pore size.

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