



Interpenetrating Network Polymer Hydrogels of Sodium Alginate and Poly(acrylic acid) for Controlled Release of Prazosin Hydrochloride

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ABSTRACT

In this study, a novel interpenetrating polymer network (IPN) hydrogel composed of crosslinked sodium alginate and poly(acrylic acid) was prepared for transdermal delivery of an anti-hypertensive drug, prazosin hydrochloride. Due to the reversible swelling behavior of the hydrogels, the synthesized networks can sense the environmental pH change and achieve an oscillatory release pattern. Using drug prazosin hydrochloride as a model molecule, the in vitro controlled drug-release behaviors of these hydrogels were investigated.

Keywords: sodium alginate, acrylic acid, drug delivery, interpenetrating network polymer.

INTRODUCTION

Drug release from solid matrices systems, made of polymer(s) and drug(s), is a basic concept for studies on controlled drug delivery. The most interesting class of polymers in this application is given by hydrogels, also pH-sensitive ones. Hydrogels are special soft and pliable polymeric materials that can be absorb large quantities of water, saline or physiological solutions while the absorbed solutions are not removable even under pressure ¹.

Hydrogels are formed from hydrophilic synthetic polymers and many natural polymers such as proteins and polysaccharides. Natural polymer gels are useful for pharmaceutical fields such as

controlled delivery devices because of their non-toxic, low cost, free availability, biocompatibility and biodegradability.

Recently, drug delivery systems based on natural hydrogels have been extensively explored to achieve the higher concentration of drugs in the specific region or tissue and the controlled release profile for extended time periods ²⁻⁵.

Interpenetrating polymer network (IPN) hydrogels are an intimate combination of two polymers both in the same network, which is obtained when at least one polymer is synthesized and/or crosslinked independently in the immediate vicinity of the other ⁶.

Prazosin hydrochloride (Fig. 1) is a widely used drug for the treatment of hypertension and congestive cardiac failure. The drug is extensively metabolized (>99%) by first pass metabolism. The bioavailability after oral administration is 57% with a shorter biological half-life of 2.9 h. Therefore, it requires multiple dosing to maintain therapeutic drug blood levels. These factors make prazosin hydrochloride, a suitable candidate for transdermal delivery, which avoids first pass metabolism, improves the bioavailability of drug, reduces the frequency of dosing and if toxic symptoms appear, the drug can be withdrawn immediately by removal of membranes. This is especially important for prazosin since there have been reports of sudden collapse after the initial dose.

In the current study we investigated the synthesis and utility of a novel type of IPN hydrogels of sodium alginate with poly(acrylic acid) for the controlled release of prazosin hydrochloride.

EXPERIMENTAL

Preparation of IPN hydrogels

The IPN hydrogels were prepared using sodium alginate (SA) and poly(acrylic acid) (PAA). The SA along with PAA was dissolved in double distilled water (total polymer concentration 5%, w/v) at 80 °C and stirred for 1 h, prazosin hydrochloride were added to the polymeric solution and stirred well to get homogeneous solution using magnetic stirrer. Then, a mixture of different quantities of formaldehyde and 1 mL of 5N HCl was added slowly and stirring was continued for 2h. The mechanism of formation of IPN structure is schematically shown in Fig 2.

Determination of drug loading

Hydrogel (0.10 g) was immersed in 10 mL of the phosphate buffer solution (pH 7.4) in a 50 mL beaker for completely swelling. The swollen hydrogels were crushed in an agate mortar with a pestle and transferred into a conical flask, and then about 20 mL of the fresh phosphate buffer solution was added to the conical flask and the homogeneous mixture was sonicated for 20 min. The prazosin hydrochloride solution was separated from the mixture after being centrifuged for 20 min at 5000 rpm. The amount of prazosin hydrochloride

was determined using UV spectrophotometer (UV-1201, Shimadzu, Kyoto, Japan). The drug loading (%) was calculated using the following equation:

$$\text{Drug Loading (\%)} = \frac{\text{Weight of drug in hydrogel}}{\text{Weight of hydrogel}} \times 100$$

In vitro drug release

The samples (0.1±0.0001 g) were immersed into 50 mL of the release medium (simulated gastric and intestinal fluids, SGF and SIF) with different pH values (pH 1.2 or 7.4) at 37°C with agitation. At given time intervals, 1 mL of the release medium was removed using a syringe attached with a 0.45 Millipore filter and after suitable dilution the concentration of released drug was measured by UV spectrophotometer at 236 nm. The drug release percent was calculated twice using the following equation:

$$\text{Released drug(\%)} = \frac{R_t}{L} \times 100$$

where L and R_t represent the initial amount of drug loaded and the final amount of drug released at time t.

RESULTS AND DISCUSSION

Drug loading efficiency

In this series of experiments, the drug loading of the hydrogels with different crosslinker content (formaldehyde) were shown in Fig 3. As can be seen, the amount of drug loaded in the hydrogel beads decrease with increasing the content of crosslinker. The greater the crosslinking density, the worse the elasticity of the polymer chains, which could restrict the penetration of prazosin hydrochloride into hydrogel, and then leads to the decrease of the loading amount for drug.

In vitro release behaviour of hydrogels

To determine the potential application of starch-based superabsorbent containing a pharmaceutically active compound, we have investigated the drug release behaviour from this system under physiological conditions. The percent of released drug from the polymeric carriers as a

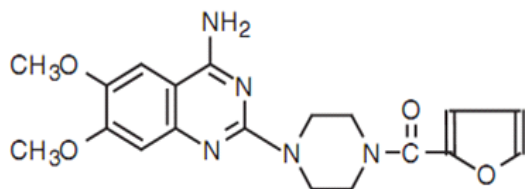
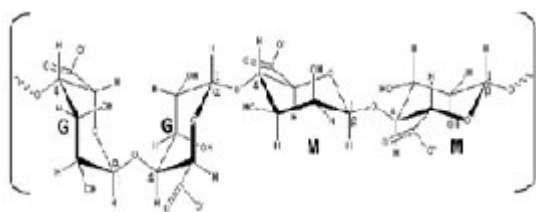
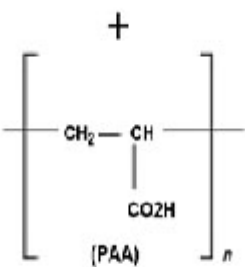


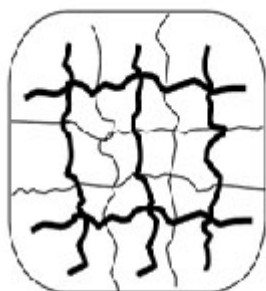
Fig.1: Chemical structure of prazosin hydrochloride.



Sodium Alginate (SA)



formaldehyde



SA-PAA IPN hydrogel



 crosslinked SA chains
 crosslinked PAA chains

Fig.2: Schematic representation of the formation of IPN structure.

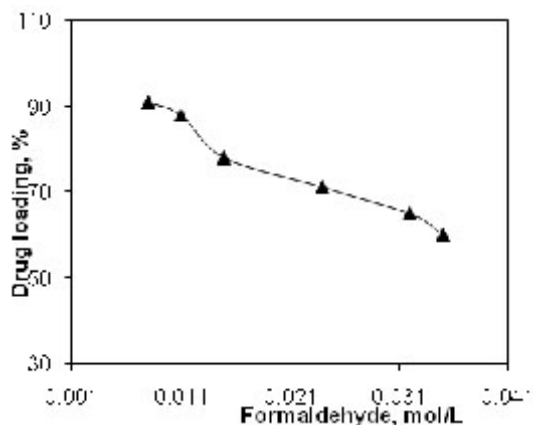


Fig.3: Effect of crosslinker content on prazosin hydrochloride loading.

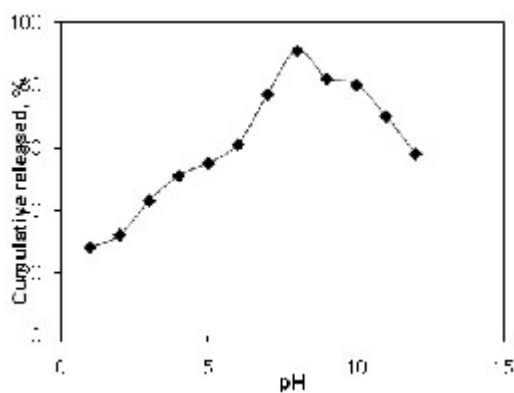


Fig.4: Release of prazosin hydrochloride from hydrogel carrier as a function of pH at 37 °C.

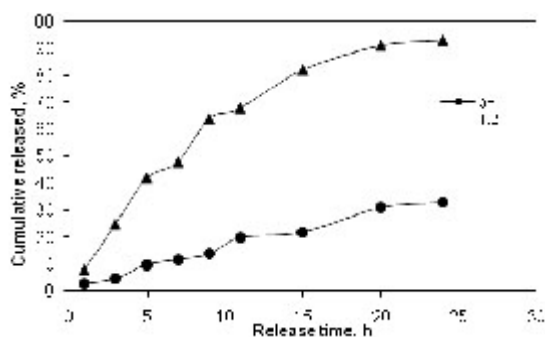


Fig.5: Release of prazosin hydrochloride from hydrogel carrier as a function of time and pH.

function of pH is shown in Fig 4. The concentration of prazosin hydrochloride released at selected time intervals was determined by UV spectrophotometer. The amount of prazosin hydrochloride released in a specified time from the starch-based hydrogels decreased at pHs lower and higher than pH 8. At acidic pH values, electrostatic repulsion between the carboxylic acid groups of backbone is low, thus decreases gel swelling and minimizes release of cephalexin via diffusion. However, in alkaline media the presence of OH⁻ increases the electrostatic repulsion between carboxylate groups, thus increases the gels swelling degree and so the release of cephalexin increased.

The release rate experiments were also performed in SFG (pH 1.2) and SIF (pH 7.4) solutions at 37 °C (Fig 5). As can be seen from Fig 5, when pH of the medium is 1.2, the cumulative release ratio of prazosin hydrochloride from the test hydrogels is below 35% at the end of the experiment (24 h), whereas almost 82% of the loaded drug is released within 15 h in pH 7.4 medium. Again, these results indicate that the higher swelling ratios of the hydrogel create larger surface areas to diffuse the drug. In basic solutions (pH 7.4), the electrostatic repulsion between COO⁻ anions of grafted poly (sodium acrylate) on the hydrogel accelerates the release of prazosin hydrochloride from the hydrogel.

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