Carbohydrate Polymers 104 (2014) 151–157

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

# Controlled release of diclofenac sodium through acrylamide grafted hydroxyethyl cellulose and sodium alginate

Ahmed A. AL-Kahtani [a,*], B.S. Sherigara [b]

[a] Department of Chemistry, Faculty of Education and Science, Albayda'a University, Rada'a 6539551, Yemen
[b] Department of Industrial Chemistry, Kuvempu University, Shankaraghatta 577451, Karnataka, India

ARTICLE INFO

*Article history:*
Received 21 October 2013
Received in revised form
30 November 2013
Accepted 5 January 2014
Available online 15 January 2014

*Keywords:*
Synthesis
Microspheres
IPN
Sodium alginate
*In vitro* release

ABSTRACT

To reinforce the hydroxyethyl cellulose for using it in biomedical and pharmaceutical applications as a drug delivery systems, the grafting of acrylamide onto hydroxyethyl cellulose (AAm-g-HEC) was achieved by Ce(IV) induced free radical polymerization. The AAm-g-HEC was then blended with sodium alginate (NaAlg) to prepare pH-sensitive interpenetrating network (IPN) microspheres (MPs) by emulsion-crosslinking method using glutaraldehyde (GA) as a crosslinking agent. The produced MPs are almost spherical in nature with smooth surfaces. Diclofenac sodium (DS), an anti-inflammatory drug, was successfully encapsulated into the MPs. The % encapsulation efficiency was found to vary between 54 and 67. The MPs were characterized by DSC, SEM and FTIR spectroscopy. *In vitro* release studies were carried out in simulated gastric fluid of pH 1.2 for 2 h followed by simulated intestinal fluid of pH 7.4 at 37 °C. The release data have been fitted to an empirical equation to investigate the diffusional exponent ($n$), which indicated that the release mechanism shifted from anomalous to the super Case-II transport.



## 1. Introduction

The interpenetrating network based pH-sensitive is an important factor in designing polymers for controlled drug release in the gastrointestinal tract (GIT). The pH of the human GIT varies from pH 1 to 3 in the stomach, 6 to 7 in the small intestine and increases to 7 to 8 in the colon (Charman, Porter, Mithani, & Dressman, 1997; Ogata et al., 1984). The pH-sensitivity of the matrix is attributed to the presence of weakly acidic and/or basic functional groups on the polymer backbone. In particular, synthetic polymers like poly(methyl methacrylate) (Bettini, Chlombo, & Peppas, 1995), poly(acrylic acid) (Ramakisson-Ganorkar, Liu, Baudys, & Kim, 1999) and natural polysaccharides such as sodium alginate (NaALg) (Wang, Turhan, & Gunasekaran, 2004) or chemically modified polysaccharides such as polyacrylamide-*g*-guar gum and polyacrylamide-grafted-alginate (Kulkarni & Sa, 2009; Soppimath, Kulkarni, & Aminabhavi, 2001), have been used as pH-sensitive drug delivery systems. Carbohydrate polymers are extensively used in recent years in biomedical and pharmaceutical applications due to their biocompatibility and biodegradability (Jana, Gandhi, Sen, & Basu, 2011; Ravi, Kumar, & Siddaramaiah, 2008; Tabata & Ikada, 1989). Hydroxyethyl cellulose (HEC) is a water-soluble cellulose ether made by swelling cellulose with NaOH and treating with ethylene oxide (Sarti, Staaf, Sakloetsakun, & Bernkop-Schnürch, 2010). The alginates harvested from sea brown algae are anionic polysaccharides consisting of linear copolymers of 1,4 a-L-guluronic (G) and 1,4 b-D-mannuronic (M) acid residues. HEC and NaALg, semi-synthetic polymers, have been extensively used in a variety of biomedical and pharmaceutical applications as they are non-expensive, non-toxics, biodegradables, biocompatibles and mucoadhesives (Davidovich-Pinhas, Harari, & Bianco-Peled, 2009; Hoemann et al., 2007; Pongjanyakul & Puttipipatkhachorn, 2007). The mechanical strength of the biopolymer can be improved by modifying it through crosslinking, grafting or blending with another polymers (AL-Kahtani, Bhojya Naik, & Sherigara, 2009; António, Ribeiro Silva, Ferreira, & Veiga, 2005; Meena, Chhatbar, Prasad, & Siddhanta, 2008; Yeom, Jegal, & Lee, 1998). The sugar residues can be modified *via* chemical or radiation treatments (Leo, Mcloughlin, & Malone, 1990; Sorour et al., 2013). Copolymers and terpolymers containing AAm offer a number of advantages, including: high permeability to both hydrophobic and water soluble solutes, increased mechanical strength, depending upon copolymer composition and crosslink density (Dalal & Narukar, 1991; Downs, Robertson, Riss, & Plunkett, 1992; Leputure, Hui, & Ropertson, 1973). DS, one of the most useful non-steroidal anti-inflammatory drugs (NSAIDs) is a practically insoluble compound in acidic solution ($pK_a$ 4.0), however, it dissolves in intestinal fluid. It has a short half-life in plasma (1–2 h). The daily dose varies between 75 and 200 mg/person, given in 3 or 4 divided portions depending on the route of administration. The most common adverse effects of the

* Corresponding author. Tel.: +967 773682802; fax: +967 6539551.
*E-mail address:* ahmeda.ahmed7012@yahoo.com (A.A. AL-Kahtani).

0144-8617/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carbpol.2014.01.018

drug are gastritis, peptic ulceration, hypersensitivity reactions and depression of renal functions (Tapia, Escobar, & Costa, 2004). Therefore, DS is an ideal model drug for preparing nonimmediate-release devices, which results in more consistent level of drug absorption and reduces the risk of local irritations compared to an immediate release devices. Besides of previously mentioned properties, NaAlg also has a susceptibility to the environmental pH and hence the incorporation of acid-sensitive drugs such as DS into MPs lead to the reduction of the gastrointestinal adverse effects which in turn results in the prevention of upper gastrointestinal tract from the irritations (Lee, Cui, Kim, Heo, & Kim, 1998; Segi, Yotsuyanagi, & Ikeda, 1989). In this study, we report the synthesis of AAm-g-HEC by grafting of acrylamide onto hydroxyethyl cellulose to enhance the properties of the matrix. The ultimate goal of this research work was to develop NaAlg and AAm-g-HEC blend IPN MPs for controlled release (CR) of DS. The IPN based systems have gained good potential to develop the controlled drug delivery systems. IPNs are any materials containing two different types of polymers, each in a network form (Davis, Siconais, Ambrosio, & Huang, 1988). The MPs formed have been characterized by variety of techniques to understand their drug release characteristics and morphological as well as chemical interactions.

## 2. Materials and methods

### 2.1. Materials

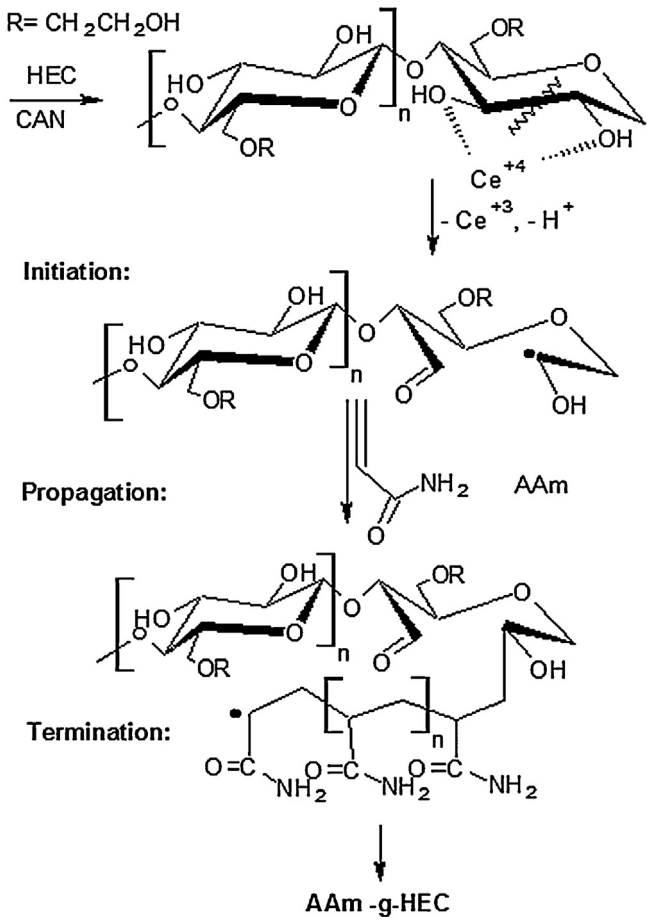
Sodium alginate (low viscosity grade sample) and glutaraldehyde (25% aqueous solution) (GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Ceric ammonium nitrate was obtained from Sigma–Aldrich Chemical Co. (St Louis, MO). Hydroxyethyl cellulose (medium molecular weight), acrylamide, light paraffin oil, n-hexane and span-80 were obtained from Loba Chemicals, Mumbai, India. DS was received as gift sample from Biocon Limited, Bangalore, India. All the chemicals were used without further purification.

### 2.2. Synthesis of acrylamide grafted onto hydroxyethyl cellulose

Acrylamide grafted onto hydroxyethyl cellulose, hereafter designed as (AAm-g-HEC) was prepared by free-radical polymerization. Briefly, 2% aqueous solution of HEC was prepared by dissolving the polymer in distilled water under constant stirring in 250 ml three-necked round bottom flask for overnight. To this solution, 0.14 mol of acrylamide and 0.005 mole of ceric ammonium nitrate solution were added and stirred well under nitrogen atmosphere for 6 h at 70 °C. The polymerized reaction mixture was then cooled, extracted by precipitated in acetone and dried under vacuum for 48 h. The proposed reaction mechanism is presented in Scheme 1.

### 2.3. Preparation of IPN MPs and drug loading

IPN MPs of NaAlg with different ratios of AAm-g-HEC, hereafter designed as NaAlg/AAm-g-HEC were prepared by emulsion-crosslinking method. The polymer solution (4%, w/v) was prepared by using gentle heat. After cooling to ambient temperature, the DS equivalent to 10, 20 and 30% (w/w) of the dry weight of polymer were dispersed in the above solution and stirred for overnight. The polymer solution containing DS was then emulsified into light liquid paraffin in the presence of 1.5% Span-80 and 1 ml of 0.1 M HCl to make the w/o emulsion. The MPs produced were hardened by adding different amounts of GA into emulsion phase. The hardened MPs separated by filtration, washed with hexane followed by water, and finally dried in a vacuum desiccator for further analysis. Totally, 12 formulations were prepared by varying three parameters, *i.e.*, %




**Scheme 1.** Proposed reaction mechanism for grafting of acrylamide AAm onto hydroxyethyl cellulose HEC using ceric ion initiation.

AAm-g-HEC, % drug loading and amount of GA. To understand the variables, formulation codes are assigned as given in Table 1. For example the formulation codes, P-xyz, refers to three variables *viz.*, *x*-represents three amounts of AAm-g-HEC numbered as 0, 1, 2 and 3 for 0%, 10%, 20% and 30% AAm-g-HEC in the IPN, *y*-represents three amount of DS drug numbered as 1, 2 and 3 for 10%, 20% and 30% DS in the IPN, *z*-represents three amount of GA numbered as 1, 2 and 3 for 3 ml, 6 ml and 9 ml of GA added. The formation of IPN structure is schematically shown in Scheme 2.

### 2.4. Estimation of % drug loading and encapsulation efficiency

Amount of DS loaded in the MPs was estimated by crushing the MPs and extracted in aqueous methanol solution by gently heated for 3 h. The solution was filtered, diluted with the buffer solution and analyzed by UV–vis spectrophotometer (Shimidzu, Japan) at $\lambda_{max}$ of 278 nm using a calibration curve. These data were collected in triplicate, but the average values (standard errors <3%) were considered in calculating the % drug loading and encapsulation efficiency. These were calculated as follows:

$$\%\text{Drug loading} = \left(\frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}}\right) \times 100 \quad (1)$$

$$\%\text{Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

These data for various formulations are presented in Tables 1 and 2.