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

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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

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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

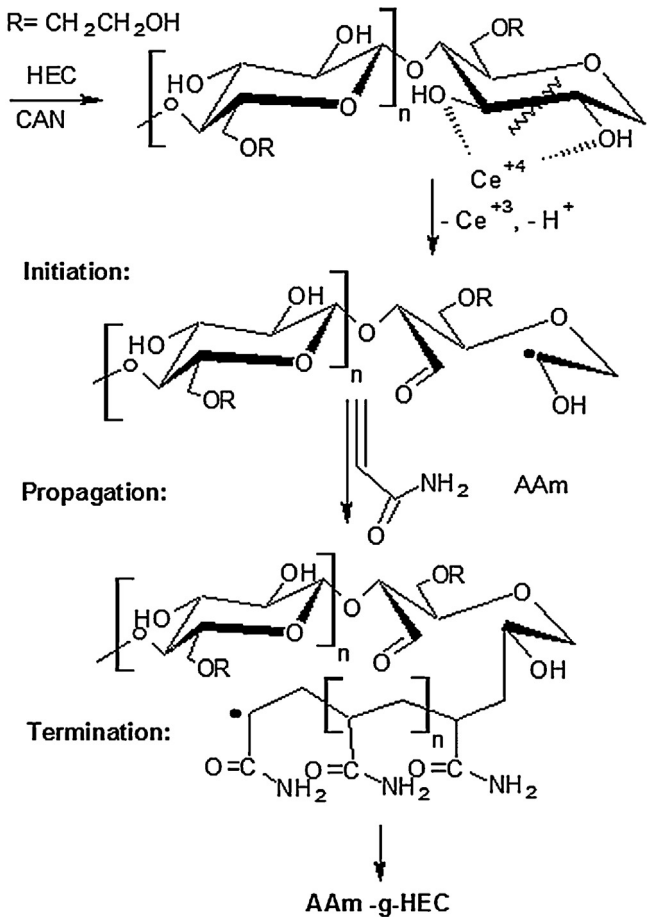
Sodium alginate (low viscosity grade sample) and glutaraldehyde (25% aqueous solution) (GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Ceric ammonium nitrate was obtained from Sigma–Aldrich Chemical Co. (St Louis, MO). Hydroxyethyl cellulose (medium molecular weight), acrylamide, light paraffin 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 λ_{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:

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

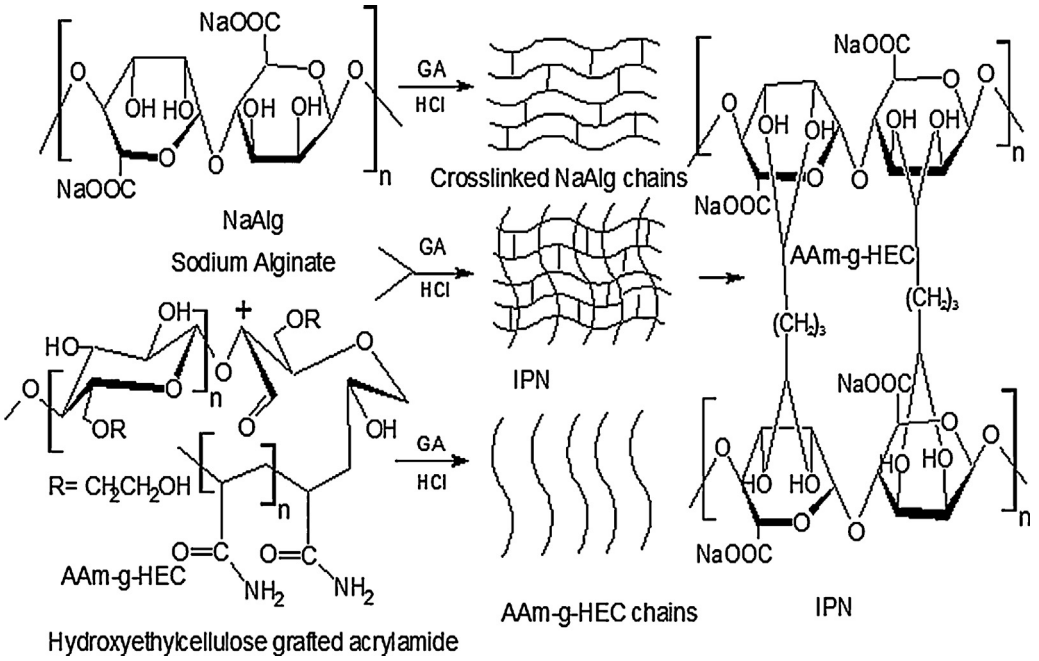
$$\%\text{Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

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

Table 1
Results of % of encapsulation efficiency, mean size of the MPs and water uptake of different formulations.

Formulation code[a]	% AAm-g-HEC in MPs	%DS loaded	%Encapsulation efficiency	Mean particle size (μm)	%Water uptake (Q)
P-012	–	10	54	201	293
P-022	–	20	54	204	293
P-032	–	30	55	206	295
P-112	10	10	58	216	298
P-122	10	20	59	218	302
P-132	10	30	60	221	308
P-212	20	10	61	234	327
P-222	20	20	61	236	341
P-232	20	30	62	239	346
P-312	30	10	63	260	345
P-322	30	20	63	262	357
P-332	30	30	64	265	372

[a] P-122 refers to formulation with three parameters, three AAm-g-HEC compositions, three DS loadings and three crosslinking amounts.



Scheme 2. Schematic representation of synthesis of IPN.

2.5. Swelling studies

Dynamic swelling of microspheres was studied by measuring the mass uptake in water. To ensure complete equilibration, samples were allowed to swell for 24 h to obtain equilibrium at 37 °C. Excess surface adhered liquid drops were removed by blotting carefully (without pressing hard) and the swollen microspheres were weighed on an electronic microbalance. The hydrogel microspheres were then dried in an oven at 50 °C for 5 h until there was no change in the weight of the dried mass of the samples. Swelling experiments were repeated thrice for each sample and the average values were used in data analysis. The standard deviations (SD) in all cases were <3%. The % water uptake (Q) was calculated as:

$$Q = \left(\frac{W_\infty - W_0}{W_0}\right) \times 100 \quad (3)$$

where W_∞ is the mass of swollen MPs and W_0 is the mass of dry MPs.

2.6. In vitro drug release study

In vitro release of DS from IPN MPs was carried out in simulated gastric fluid of pH 1.2 for the initial 2 h and then in simulated intestinal fluid of pH 7.4, until completion of dissolution maintained at 37 °C. The experiments were carried out using the USP-I dissolution tester (Dissotest, Lab India, Mumbai). Into 500 ml of the dissolution fluids was introduced 100 mg of each sample and stirred at 100 rpm. At regular intervals of time, aliquots of 5 ml were withdrawn and analyzed for DS at λ_{max} value of 278 nm using a UV–vis Spectrophotometer (Shimidzu, Japan). Dissolution medium was maintained at constant volume by replacing the samples with a fresh dissolution medium.

Table 2
Results of % of encapsulation efficiency, mean particle size and water uptake of formulations crosslinked with different amount of GA.

Formulation code	Crosslinking agent (GA in ml)	%Encapsulation efficiency	Mean particle size (μm)	%Water uptake (Q)
P-221	3	55	260	366
P-222	6	61	236	341
P-223	9	67	183	171

2.7. Fourier transform infrared (FTIR) spectra

FTIR spectra of plain NaAlg, MPs of NaAlg with AAm-g-HEC were measured using Shimadzu-1800S spectrophotometer at 2 cm^{-1} resolution with 64 scans over the spectral range from 4000 to 400 cm^{-1}. All the samples were crushed with potassium bromide and pellets were obtained by applying a pressure of 600 kg/cm^2 using FTIR pellet maker.

2.8. Differential scanning calorimetric (DSC)

For the differential scanning calorimetric (DSC) measurements, a Perkin-Elmer DSC-7, operating in a dynamic mode was employed. Nitrogen gas was used as an inert gas at a flow rate of 20 ml/min. Each sample (80 mg) of (a) plain DS (b) drug loaded MPs and (c) placebo MPs were placed in aluminum pan. An empty aluminum pan was used as a reference and a heating/cooling rate of 10 °C/min was applied throughout the study with scan ranges between 0 and 300 °C.

2.9. Scanning electron microscopic (SEM)

SEM micrographs of the MPs were measured using a JEOL model JSM-840A scanning electron microscope (Japan) and micrographs were taken at the required magnification. A working distance of 19 mm was maintained and the acceleration voltage used was 20 kV with the secondary electron detector for imaging (SEI).

2.10. Particle size measurements

Particle size of the MPs was measured using optical microscopy (Swift Prior, UK, transmitted light microscope instrument). About 200 mg of MPs were dispersed into 100 ml of methanol and stirred under sonication for 2 min to remove agglomerations of MPs. For measurement of sizes of different formulations, the sample holder was cleaned with distilled water followed by acetone to prevent cross contamination. The mean particle size (μm) was recorded and these results are included in Tables 1 and 2.

3. Results and discussion

3.1. Preparation and characterization of MPs

Grafting of AAm onto HEC was achieved by Ce(IV) induced free radical polymerization. The complex formed with the —OH groups of HEC at the C-2 and C-3 position decomposes to generate the free radical site, facilitating the grafting to occur at the active site of HEC with the incoming AAm monomer. The proposed reaction mechanism is shown in Scheme 1. The drug-loaded MPs of NaAlg and AAm-g-HEC were prepared by crosslinking with GA. The effects of graft copolymer content and GA on encapsulation efficiency of DS loaded MPs are presented in Tables 1 and 2. It is indicated that, as the AAm-g-HEC content in the matrix was increased from 10 to 30%, encapsulation efficiency increased from 59 to 63% for formulations, P-122 to P-322 respectively. It is also noticed that as the amount of GA in the matrix was increased from 3 to 9 ml, encapsulation efficiency increased from 55 to 67% for formulations, P-221 to P-223 (Table 2).

The size of particles ranged from 183 to 265 μm. The results included in Table 1 show that with an increase in graft copolymer content in the matrix, an increase in particle size was observed. This can be explained by the fact that at higher amounts of AAm-g-HEC, the viscosity of polymer solution increased, thereby producing bigger droplets during emulsification (AL-Kahtani et al., 2009). However, the particle size was decreased with increasing crosslinking content. This was due to the shrinkage of particles during the microsphere formation at higher amount of GA, thereby reducing their sizes (Korsmeyer & Peppas, 1981; Krishna Rao, Vijaya Kumar Naidu, Subha, Sairam, & Aminabhavi, 2006).

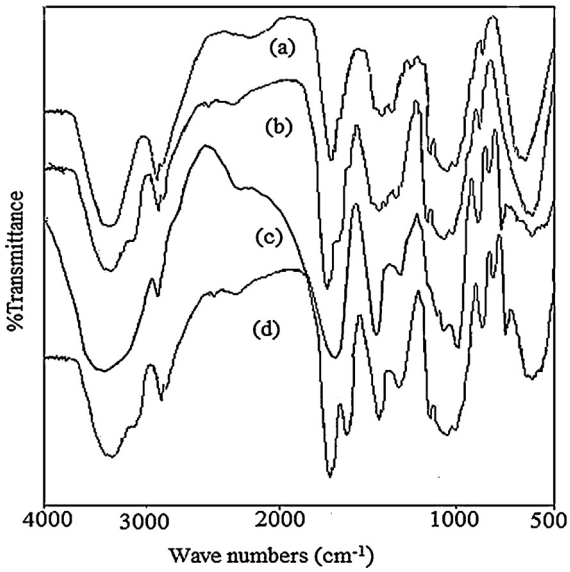


Fig. 1. FTIR spectra of (a) plain HEC, (b) AAm-g-HEC, (c) plain NaAlg and (d) placebo MPs.

3.2. Fourier transform infrared (FTIR) spectra

Fig. 1 shows the FTIR spectra of (a) plain HEC, (b) AAm-g-HEC, (c) plain NaAlg and (d) placebo MPs. As can be seen, in the spectrum of HEC, a broad band at 3440 cm^{-1} is due to O—H stretching vibrations. The O—H bending is seen at 1355 cm^{-1}. Aliphatic C—H stretching and bending vibrations are indicated by bands at 2929 and 1429 cm^{-1}. Bands at 1020 and 1050 cm^{-1} represent the C—O—C stretching vibrations, while band at 1145 cm^{-1} is attributed to C—O stretching vibrations. In the case of AAm-g-HEC, all the bands observed in HEC have appeared in addition to a new shoulder band observed at ~3200 cm^{-1} and a sharp band around ~1665 cm^{-1} corresponding to —NH and C=O stretching vibration, indicating the grafting reaction. In the case of NaAlg, as can be seen in the spectrum, a broad band at 3440 cm^{-1} is due to O—H stretching vibrations. The characteristic peak of sodium alginate appeared at 819 cm^{-1} (Na—O) and two peaks at 1616 and 1440 cm^{-1} for the associated carboxylic acid salt (—COO— antisymmetric stretch). The (C=O stretching) is seen at 1050 cm^{-1}. In the case of placebo MPs, all the bands of both NaAlg and AAm-g-HEC were observed in addition to a new band observed at 1184 cm^{-1} due to the ether linkage formed as a result of the crosslinking reaction between hydroxyl groups of NaAlg and aldehyde groups of GA. A reaction leading to the formation of crosslinking is depicted in Scheme 2.

3.3. Differential scanning calorimetry (DSC)

DSC thermograms of (a) pristine DS, (b) plain MPs and (c) drug-loaded MPs are displayed in Fig. 2. The DSC thermogram of DS showed a sharp endothermic peak at 229.35 °C due to polymorphism and melting of DS. In case of drug-loaded microspheres, all the peaks observed in placebo microspheres are noticed, but there was no characteristic peak corresponding to DS, indicating that the most of drug was molecularly dispersed in the polymer matrix.

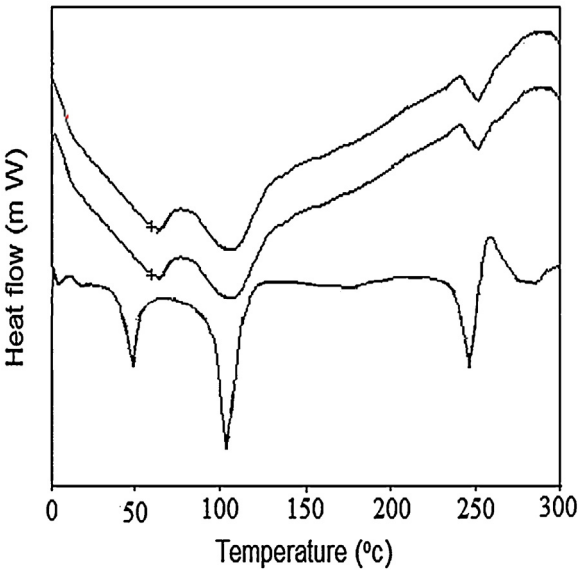


Fig. 2. DSC thermograms of (a) pristine DS, (b) plain MPs and (c) drug-loaded MPs.

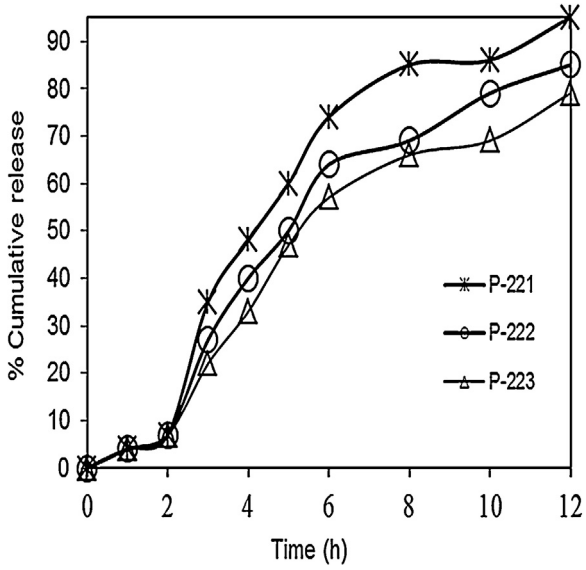


Fig. 4. Effect of different crosslinking on *in vitro* release profiles in the pH-change system for formulations, P-221, P-222 and P-223.

3.4. Scanning electron microscopy (SEM)

SEM images of single microspheres taken at 200 magnifications are shown in Fig. 3. The microspheres produced were almost spherical in nature with smooth surfaces, however, the polymeric debris seen around some particles could be due to the type of polymers or the method of particle production.

3.5. Swelling studies

MPs produced with different extent of crosslinking and graft copolymer ratio were subjected to dynamic swelling studies in water by mass uptake measurements with time. These data are displayed in Tables 1 and 2. The % water uptake was decreased with increasing crosslinking agent in the matrix. For instance, with increasing amount of GA from 3 to 9 mL, % water uptake decreased from 366 to 171 (formulations, P-221 to P-223). The reduction in water uptake may be due to the formation of a rigid network structure at higher extent of crosslinking. However, the % water uptake was increased by increasing graft copolymer content in the matrix with increasing amount of HEC-g-AAm from 10% to 30%, equilibrium water uptake was increased from 218% to 262% (P-122 to P-322). The higher water uptake could be due to the extremely hydrophilic nature of HEC-g-AAm/NaAlg polymer matrix.

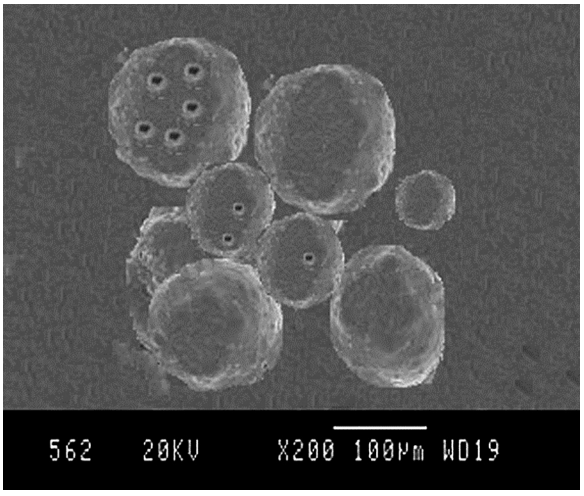


Fig. 3. SEM micrographs of DS loaded group MPs.

3.6. In vitro drug release

To understand the release of DS from the IPN MPs, *in vitro* release experiments were carried out in simulated gastric fluid of pH 1.2 for the initial 2 h, then in simulated intestinal fluid of pH 7.4, for 10 h. When analyzing the release profile of drugs like DS, the dependence of solubility on pH must be taken in to account. In fact, DS presents a higher solubility in water as salt, but in artificial gastric solution (pH 1.2) DS is converted into its ionized form, which is well known to be practically insoluble in the stomach (Kincl, Vrečer, & Veber, 2004; Sheu, Chou, Kao, Liu, & Sokoloski, 1992). In addition, alginate at low pH is protonated into insoluble form of alginic acid this displays properties of swelling that explains low amount of release (Fernandez-Hervas, Holgado, Fini, & Fell, 1998). As can be seen, No significant drug release from all formulations for the first 2 h in acidic media (pH 1.2). However, when the dissolution was changed to pH 7.4, the DS release rate from all formulations was slightly increased. The *% in vitro* release time plots for the drug-loaded MPs for formulations, P-221, P-222 and P-223 are shown in Fig. 4 to illustrate the effect of pH and crosslinking on *in vitro* release profiles. The *% in vitro* release was decreased with increasing GA content in the matrix. This is due to the formation of a more tightly crosslinked rigid network structure as the amount of crosslinking agent has increased from 3 to 9 ml. The effects of polymer compositions on release rates are presented in Fig. 5. As can be seen, the *% in vitro* release was increased with increasing % AAm-g-HEC in the matrix. The results can be explained according to the fact that with increasing AAm-g-HEC content in the matrix, swelling of the matrix also increased due to the extremely hydrophilic nature of AAm-g-HEC, which in turn facilitates the penetration of water molecules into the loaded gel and subsequently enhances the amounts of DS released. Similarly, the *% in vitro* release was increased with increasing % drug loading in the matrix (Fig. 6). The release rate becomes quite slower at the lower amount of drug in the matrix, due to the availability of more free void spaces through which a lesser number of drug molecules could transport.

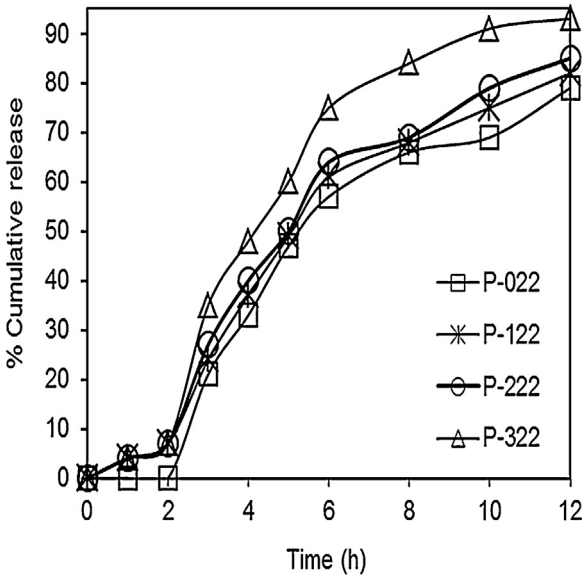


Fig. 5. Effect of different blend composition on *in vitro* release profiles in the pH-change system for formulations, P-022, P-122, P-222 and P-223.

3.7. Drug release kinetics

The release data were investigated by fitting the cumulative fraction release data, M_t/M_∞, to an empirical equation (Lee, 1985; Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \quad (3')$$

Here, M_t and M_∞ represent the amount of DS released at time t and at infinite time, k is a constant characteristic of the drug–polymer system and n is the diffusional exponent which suggests the nature of the release mechanism. The values of k and n have been calculated by the least squares method from the results of $\log(M_t/M_\infty)$ *versus* $\log t$. These data along with the values of correlation coefficient r are presented in Table 3. As observed from the table, correlation coefficient (r) values approached unity, suggesting a best fit to the Fickian model. The values of k decreased with increasing crosslink agent and increased with increasing graft copolymer content in the matrix. The k-values ranging between 0.060 and 0.145, indicating mild-type of interactions between the drug and the polymer matrices. The values of n lie between 0.94 and 1.46, indicating a shift from anomalous to super Case-II transport. It is noticed that as the amount of crosslinking was increased from 3 to 9 mL, the values of n increased from 1.05 to 1.39, indicating that the drug release from MPs follows the super Case-II transport (P-221, P-222 and P-223). The values of n being higher for MPs crosslinked with 9 ml of GA could be due to the formation of a rigid IPN matrix. It is also noted that as the amount of AAm-g-HEC content in the matrix was increased from 10 to 30%, the values of n increased from 1.21 to 1.49 (P-122, P-222 and P-322). However, the MPs prepared by varying the amount of DS in the matrix from 10 to 30 wt% keeping AAm-g-HEC (20%) and GA (6 ml) constant, exhibited n values ranging from 1.49 to 0.94, indicating a shift from super Case-II to an anomalous transport (P-212, P-222 and P-232).

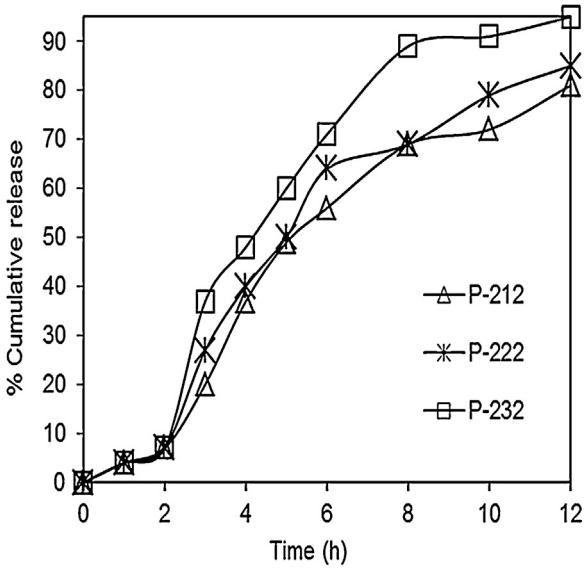


Fig. 6. Effect of % drug loading on *in vitro* release profiles of DS in the pH-change system for formulations, P-212, P-222 and P-232.

Table 3
Release kinetics parameters of different formulations.

Formulation code	k	n	r^2
P-221	0.116	1.05	0.99
P-222	0.085	1.21	0.99
P-223	0.060	1.39	0.99
P-022	0.046	1.46	0.99
P-122	0.085	1.34	0.99
P-222	0.094	1.21	0.99
P-322	0.151	1.05	0.99
P-212	0.060	1.49	0.96
P-222	0.095	1.21	0.99
P-232	0.145	0.94	0.98

4. Conclusions

The hydrophilic nature of acrylamide modified hydroxyethyl cellulose was utilized to develop blend microspheres with another hydrophilic carbohydrate polymer *viz.*, sodium alginate by water-in-oil emulsification technique using GA as a crosslinking agent. The release of drug from the MPs was dependent upon of % AAm-g-HEC, % drug loading, the extent of GA and the pH medium.

DS drug was successfully encapsulated into the MPs and encapsulation efficiency up to 67% was obtained. Microspheres were produced with a narrow size distribution in the sizes ranging from 183 to 265 μm. The values of n lie between 0.94 and 1.49, indicating a shift from anomalous to the super Case-II transport. The covalent crosslinking of the blend with glutaraldehyde leads to reduce swelling and introduce specific properties such as structural strength along with thermal and mechanical stability. The swelling studies have shown that with increasing amount of AAm-g-HEC in the MPs, % water uptake was increased. This effect is correlated with the release rates of the drug through the MPs containing different amount of AAm-g-HEC. FTIR confirmed the grafting reaction and formations of MPs. DSC has confirmed the uniform molecular distribution of the drug in the polymer matrix.

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