



Hydroxypropyl methyl cellulose grafted with polyacrylamide: Application in controlled release of 5-amino salicylic acid

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ABSTRACT

In the present study, hydroxypropyl methyl cellulose grafted with polyacrylamide (HPMC-g-PAM) hydrogel was evaluated in vitro as a potential carrier for controlled release of 5-amino salicylic acid (5-ASA). The graft copolymer was developed by grafting PAM chains onto HPMC backbone using potassium persulphate as initiator. The swelling behaviour of hydrogel based tablet was investigated as a function of pH and time in various buffer solutions similar to that of gastric and intestinal fluids. The % equilibrium swelling was found to be higher in case of simulated intestinal fluid (pH = 7.4) and lower in simulated gastric fluid (pH = 1.2), making an ideal matrix as required for colon specific drug delivery. The drug release study was performed at various pH values akin to the condition of GI tract. The release kinetics of 5-ASA showed non-Fickian diffusion behaviour. This indicates that the release is controlled by a combination of polymer relaxation or erosion of the matrix and diffusion of the drug from the swollen matrix.

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1. Introduction

Polymeric hydrogels have led to significant advances in pharmaceutical and biomedical fields for controlled release of drugs [1–8], especially those which are able to swell and shrink in response to environmental stimuli like pH, temperature, ionic strength, etc. [9]. Out of stimuli responsive polymers, pH-sensitive hydrogels are extensively used in the field of drug delivery [9]. The high water content of hydrogel makes it to be flexible [10]. Peppas and Peppas have pointed out that the presence of moieties with carboxylic or acrylamide groups is responsible for pH dependent behaviour of polymer systems [11]. The cross linking in hydrogel results in formation of an insoluble network structure, which facilitates swelling and hydration of polymeric gel in simulated body fluid without complete dissolution of the polymer [12]. The ability of drug molecules to diffuse into and out from hydrogels makes it efficient as matrix for drug delivery systems for different routes of administration. Out of various modes of drug delivery, the oral delivery is a widely accepted route of administration for therapeutic drugs. The gastrointestinal tract is divided into stomach, small intestine and large intestine. The pH varies widely along the gastrointestinal tract. It varies from a low pH 1.2 to 1.4 (fasting condition) in stomach to 7.4 in colon region. The acidic environment combined with various enzymes is responsible for the degradation of peptides and many other drugs in stomach [13,14]. An ideal drug delivery

matrix for oral delivery should protect the drug from the low pH harsh environment of the stomach and then be abruptly released into the proximal colon (i.e. in lower gastrointestinal tract). Consequently, the matrix should have lower rate of drug release in acidic pH, and higher in neutral/alkaline pH conditions.

Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical and biomedical fields for controlled release application. The polysaccharides have advantages over synthetic polymers, primarily because they are non-toxic, less expensive, biodegradable and freely available [15]. However, natural polymers also possess some drawbacks, such as uncontrolled rate of hydration, microbial contamination, and drop in viscosity on storing. Fortunately, there are strategies to overcome these drawbacks by suitable chemical modification. Hence it is not surprising that hydrogels of several modified natural polymers already find potential application in sustained drug delivery and other fields [15–20]. The conjugation of natural polymers with synthetic polymers is of great interest because of its wide range of applications in diversified fields. Of late, an expanding interest has been devoted to the synthesis of chemically modified polysaccharides through grafting which combine the advantages of both synthetic and natural polymers. Graft copolymerization of vinyl monomers onto natural polysaccharides is one of the most promising techniques, as it functionalizes these biopolymers to their potential by imparting desirable properties onto them [21,22].

One of the prominent modified natural polysaccharide, HPMC is widely used in the field of biomedical science [23–25]. In our previous study [26], we have explained the synthesis and detailed characterization of PAM grafted HPMC based hydrogel. The present

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study reflects the use of this hydrogel as the controlled release carrier for 5-ASA for pH specific drug delivery. The experiment has been conducted under simulated conditions, resembling GI tract environment.

2. Materials and methods

2.1. Materials

Hydroxypropyl methyl cellulose was purchased from Lancaster, UK. Acrylamide and sodium hydroxide were procured from E. Mark, Mumbai, India. Potassium persulphate of analytical grade was supplied by Qualigens Fine Chemicals, Mumbai, India. 5-Amino salicylic acid (AR Grade) was acquired from Spectrochem Pvt. Ltd., Mumbai, India. Analytical grade acetone and hydroquinone were obtained from S. D. Fine Chemicals, Mumbai, India. All chemicals were used as received, without further purification.

2.2. Preparation of hydroxypropyl methyl cellulose grafted with polyacrylamide hydrogel

The graft copolymerization of polyacrylamide and HPMC was carried out in a 250 mL three necked round bottom flask, in inert atmosphere of nitrogen using potassium persulphate as free radical initiator. The detailed procedure and reaction conditions have been reported in our earlier study [26].

2.3. Determination of molecular weight and molecular weight distribution using gel permeation chromatography

Molecular weight and molecular weight distribution of HPMC and various graft copolymers were determined using a GPC system (Model: 2414; Make: Waters (I) Pvt. Ltd., USA). The mobile phase was in aqueous solution (HPLC grade water was used for this analysis). The polymer solution was filtered through Whatman syringe filter (0.45 μm) before it was injected into the column. The flow rate of injection was fixed at 0.6 mL/min, and the column temperature was kept at 30 °C during the analysis.

2.4. Preparation of tablets

The polymer matrices (HPMC and HPMC-g-PAMs) were finely ground in a blender, with the model drug (5-ASA) and a binder (guar gum) in 10:1:0.3 ratio. The mixture was wetted with ethanol and mixed further. The paste was dried at 50 °C to a constant weight and ground. Then a mixture of silicon-di-oxide and magnesium stearate (2:1 ratio) was added as lubricant, in amount not exceeding 3% of the ground powder. After mixing and sieving (20 mesh), tablet of 250 mg was prepared using tablet making machine. The drug loading of each tablet was 22.123 mg.

2.5. Swelling and erosion test

The equilibrium swelling behaviour of tablets was measured at 37 °C in buffer solutions of pH similar to that of gastric and intestinal fluids. A small pre-weighed piece of tablet was immersed in 100 mL of buffer solutions at 37 °C for 24 h. Later, the swollen piece was blotted with filter paper and weighed again. The ratio between the swollen and dry weight, is defined as the extent of swelling (P_s), was calculated using Eq. (1).

$$P_s = \frac{\text{Weight swollen gel} - \text{weight of dried gel}}{\text{Weight of dried gel}} \times 100 \quad (1)$$

During drug release, some tablets disintegrated partially. The percentage erosion (% D) was calculated using Eq. (2) based on the difference between initial dry weight of the tablet (W_i) and dry

weight of the tablet (W_d) at time t , considering drug release at time t (M_t/M_∞).

$$D(t) = \frac{W_i - W_{d(t)} - W_d(1 - (M_t/M_\infty))}{W_i} \times 100 \quad (2)$$

where M_t is the amount of drug release at time t ; M_∞ is the total amount of drug released after infinite time; and W_{drug} is the initial weight of drug.

2.6. In vitro study of drug release

The in vitro release of entrapped drug (5-ASA) was determined in various buffer solutions-simulating gastric fluid (pH 1.2) and simulating intestinal fluid (pH 7.4), at 37 °C. The controlled drug release study was conducted using USP rotating paddle method (using Drug dissolution Apparatus; Model – 1912, EI, India). The tablet was immersed in 900 mL of buffer solution, maintained at 37 °C, under a constant rotation of 60 rpm. At definite time intervals (every 1 h), an aliquot was withdrawn and its absorbance was measured (λ_{max} : 303 nm at pH 1.2, and λ_{max} : 331 nm at pH 7.4) spectrophotometrically (using UV-Visible Spectrophotometer – Model UV-1800, Shimadzu, Japan). The withdrawn sample was replaced with an equal volume of fresh buffer, to keep the volume of release media constant. The amount of drug at any selected time was calculated from 5-ASA calibration curve. The rate of drug release is graphically represented in form of drug release profile (% cumulative drug release vs. time).

3. Results and discussion

3.1. Synthesis and characterization

Polyacrylamide grafted hydroxypropyl methyl cellulose has been synthesized by radical polymerization technique, where potassium persulphate was used as initiator [26]. The mechanism of formation of graft copolymer is based on the fact that the initiator generates free radical sites on polysaccharide backbone and grafting of polyacrylamide took place onto these free radical sites, so generated. The detailed mechanism as well as different characterizations of the synthesized graft copolymer has been explained in our earlier report [26]. By altering reaction parameters such as temperature, initiator concentration and monomer concentration, various grades of graft copolymers have been obtained and optimized the best one (HPMC-g-PAM 10) with respect to % equilibrium swelling and t_{50} (time taken for release of 50% drug from the hydrogel based matrix) value as shown in Fig. 1.

The molecular weight, molecular weight distribution of HPMC and various graft copolymers were determined by GPC analysis and the results are reported in Table 1 (as well as in Figs. S1 and S2, Supporting Information). It is obvious from the result that all graft copolymers are having higher molecular weight than HPMC. This is due to the presence of grafted PAM chains onto HPMC backbone. Further, out of various graft copolymers, HPMC-g-PAM 10, which is having highest % GE, showed maximum molecular weight. This is because of the fact that higher is the % GE, longer would be the grafted PAM chains [26], which will increase the molecular weight.

3.2. Swelling and erosion characteristics of the hydrogel based tablet

The % equilibrium swelling and erosion behaviour of tablets have been investigated and results are presented in Table 2. The optimum swelling and erosion behaviour is essential for uniform and prolonged release of the drug from the matrix. The swelling characteristics and drug release behaviour of a polymeric hydrogel

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