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Modified hydroxypropyl methyl cellulose: Efficient matrix for controlled release of 5-amino salicylic acid

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ABSTRACT

Hydroxypropyl methyl cellulose has been modified by grafting synthetic polyacrylamide chains [g-HPMC (M)] in presence of microwave irradiation, which has used as carrier for controlled release of 5-amino salicylic acid (5-ASA). The FTIR and UV–vis–NIR studies reveal the excellent compatibility between g-HPMC (M) and 5-ASA. Field emission scanning electron microscopy (FESEM) and UV–vis–NIR analyses suggest that physical interaction predominates between the drug and matrix. % equilibrium swelling ratio (% ESR) of g-HPMC (M) decreased with addition of salt solutions and follow the order: $Na^+ > K^+ > Mg^{2+} > Ca^{2+} > Al^{3+}$. The in vitro 5-ASA release studies indicate that g-HPMC (M) delivers the drug preferentially in colonic region in more sustained way than that of HPMC. The 5-ASA release follows first order kinetics and non-Fickian diffusion mechanism. These favorable features make the graft copolymer a potential matrix for colon specific delivery of 5-ASA.

1. Introduction

In recent years, polymeric materials have gained significant attention for the delivery of various therapeutic agents. Biodegradable polymers are widely used for encapsulating drugs and their subsequent release behaviour [1–6]. Recently, targeted or site-specific drug delivery [7–9] is one of the major challenge in disease therapy. Among the various modes of drug delivery, oral mode is the most suitable and commonly employed route owing to its ease of administration, cost effectiveness, high patient compliance, and flexibility in the design of dosage form [10–14]. Site-specific drug delivery to the colonic region has great importance in the field of pharmacotherapy. Several colonic diseases such as inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease can be treated more effectively by local delivery of anti-inflammatory agents to the large intestine [15–18]. However, the systemic absorption of drugs from the upper part of the gastrointestinal tract of the human body may causes side effects. These can be eliminated or reduced by protecting the drug release prior to its entry in colonic region. An ideal colon specific drug delivery system should protect the release of drug from the acidic pH of the stomach. Simultaneously, it should release the drug rapidly into the proximal colon (i.e. in lower gastrointestinal tract). Thus, the pH-responsive polymeric systems would be preferable for the colon targeted drug delivery [19–23].

5-Amino salicylic acid (5-ASA) is also known as mesalamine, which belongs to the category of amino derivative of salicylic acid. It is an active component of azulfidine, a combination of a sulfa drug. 5-ASA is used as an anti-inflammatory drug. The immune system in our human body locates and destroys harmful substances, called antigens (such as bacteria, viruses, poisons). Inflammation is one of the basic tools of our immune system which can protect our bodies from bacteria, viruses, microbes and other foreign substances. Immune system (specifically white blood cells) produces certain disease-fighting chemicals and sends them to the areas of the body affected by the antigens. The chemicals fight the antigens, but at the same time also cause the redness, swelling, and pain which we recognize as symptoms of inflammation. This medication (5-ASA) is effectively used to treat ulcerative colitis, helps to reduce rectal bleeding, stomach pain and also mild to moderate Crohn's disease. 5-ASA works to diminish the overgrowth of bacteria in the body, particularly in the colonic region that causes inflammation, tissue damage and diarrhea. As a derivative of salicylic acid, mesalamine is also considered as antioxidant that traps free radicals, which potentially damaged the by-products of metabolism.

From last few decades, cellulose derivatives [24,25] are extensively used in controlled drug release applications. Hydroxypropyl methyl cellulose (HPMC), one of the most important cellulose derivatives are used frequently as a carrier for controlled release of drugs in tablet formulations [26–29]. However, the use of

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unmodified polysaccharides has certain limitations in drug delivery applications such as faster rate of drug release, higher rate of erosion and so on. To overcome these limitations and modify the polysaccharides, several methods have been developed. Grafting is one of the most important methods for the synthesis of modified biopolymer/natural polymers for controlled drug delivery applications.

Recently in authors' laboratory, various modified polysaccharides have been developed and used as matrices for controlled release of model drugs [30–33]. More recently, we have designed a novel pH sensitive graft copolymer derived from HPMC and poly (acrylamide) in presence of microwave irradiation [30]. Out of various techniques, microwave irradiation based grafting process improves the reaction rate and % grafting efficiency (% GE). The electromagnetic irradiation selectively excites the polar bonds compared to the non-polar bonds of polysaccharides which results in the cleavage/breakage of only polar bonds. This results free radical sites for grafting on polysaccharide surface without cleavage of C—C bond. Subsequently, the product selectivity was enhanced in compared to conventional chemical grafting method. It was also explained before that higher the % GE, better would be the efficacy as matrix for controlled release of drugs [33]. Thus in one hand, HPMC because of its natural abundance, presence of hydroxyl groups, inexpensive and biocompatible nature, and on the other hand polyacrylamide can play important role for stimulus responsive behaviour, the developed copolymer i.e. g-HPMC (M) probably be a suitable candidate for colon specific drug carrier.

Herein, we report the application of polyacrylamide modified HPMC developed by microwave irradiation [g-HPMC (M)] for controlled release of colonic drug – 5-ASA. The synthesized hydrogel seems to be a potential candidate for 5-ASA carrier as it demonstrates the supplementary requirements such as excellent compatibility with the drug (as evidenced from UV–vis–NIR, FTIR and FESEM analyses), better swelling characteristics [30], pH-responsive behaviour, non-cytotoxic and biodegradable nature [30]. The details of drug release mechanism and kinetics has also been explored. The in vitro release profiles suggest that g-HPMC (M) releases 5-ASA in a more sustained way than that of neat HPMC.

2. Materials and methods

2.1. Materials

HPMC (Lancaster, UK), acrylamide (E. Merck, Mumbai, India), potassium persulphate (Qualigens Fine chemicals, Mumbai, India), 5-ASA (AR Grade, Spectrochem Pvt. Ltd. Mumbai, India), acetone (S. D. Fine chemicals, Mumbai, India), hydroquinone (S. D. Fine chemicals, Mumbai, India) were used as received, without further purification.

2.2. Preparation of g-HPMC (M) in presence of microwave irradiation

The graft copolymer [g-HPMC (M)] was developed by free radical polymerization using microwave irradiation. The reaction was performed at a temperature of 70 °C in presence of 900 W microwave irradiation and potassium persulphate initiator. The details of reaction conditions and procedure have been described in our previous report [30]. The homopolymer (i.e. polyacrylamide), which was formed during the copolymerization reaction was separated through solvent extraction method (using 1:1 formamide/acetic acid) [30]. By variation of reaction parameters, series of graft copolymers [g-HPMC (M)] were synthesized and optimized the best one with respect to higher % GE and lower % equilibrium swelling ratio [30]. Here the optimized copolymer i.e. g-HPMC 6 (M) has been further characterized and used it as matrix for in vitro controlled release of 5-ASA.

2.3. Characterization

FTIR spectra of g-HPMC (M), 5-ASA and tablet formulations were recorded in solid state using FTIR spectrometer (IR-Perkin Elmer, Spectrum 2000, USA). Solid state UV–vis–NIR study was performed using Cary series UV–vis–NIR Spectrophotometer (Cary–5000). The TGA and DTG analyses of g-HPMC (M) were executed using a thermogravimetric analyser (Shimadzu DTG–60) with a heating rate of 10 °C/min under nitrogen atmosphere. The surface morphologies of the copolymer, 5-ASA and the tablet formulation were carried out in dry state using field emission scanning electron microscopy (FESEM Supra 55, Make – Zeiss, Germany).

2.4. Swelling characteristics in various salt solutions

The extracellular fluids of the human body contain various ions including sodium, potassium, calcium, chloride, hydrogen carbonate. Whereas, the plasma contains mineral ions like Na^+, K^+, Mg^{2+}, HCO_3^-, Cl^-. Thus it is essential to observe the effect of various salts on swelling behaviour of the hydrogels for drug delivery applications. Because of the interactions between hydrogel and salt cations, it may affect the rate of swelling of the hydrogel. Besides it was also observed that the drug release is directly proportional to the swelling behaviour of the hydrogel.

For this purpose, the equilibrium swelling characteristic of g-HPMC (M) was carried out in aqueous media and different salt solutions (LiCl, NaCl, KCl, $MgCl_2$, $CaCl_2$, $BaCl_2$, $AlCl_3$) through gravimetric method. A known weight of dried polymer [g-HPMC (M)] was taken and immersed into 100 mL of water or in various salt solutions for 24 h at a constant temperature (37 °C). After a certain time interval (every 3 h) swollen polymer was withdrawn, wiped with tissue paper to remove excess of solvent, and then reweighed. The equilibrium swelling was attained at ~21 h. The % swelling (Ps) of g-HPMC (M) was calculated using Eq. (1) [30,31].

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

2.5. Determination of % erosion

Rate of drug release from polymer matrix also depends on the erosion of matrix. It is presumed that erosion of the polymer matrix starts once 'critical gel concentration' attained [32]. The % erosion (% ER) was determined using Eq. (2) [32].

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

where, W_i is the initial weight of the dried tablet, W_d is the weight of the dried tablet at time t, W_{drug} is the initial weight of the drug, M_t/M_∞ is the fraction of drug release at time t.

2.6. In vitro 5-amino salicylic acid (5-ASA) release study

2.6.1. Preparation of tablet

450 mg of g-HPMC (M) as matrix, 50 mg of guar gum as binder and 500 mg of 5-ASA was used for the tablet preparation. The tablet was prepared in the same method as reported previously [30,32].

2.6.2. 5-Amino salicylic acid release study

The in vitro release of loaded 5-ASA drug from neat HPMC and g-HPMC (M) was investigated using dissolution apparatus (Lab India, Model: DS 8000) with constant rotation of 60 rpm at 37 ± 0.5 °C using 900 mL various buffer solutions related to simulated gastric