International Journal of Biological Macromolecules 94 (2017) 691–697

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Effect of Ca^{+2} ion on the release of diltiazem hydrochloride from matrix tablets of carboxymethyl xanthan gum graft polyacrylamide

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ARTICLE INFO

Article history:
Received 31 July 2016
Received in revised form 28 August 2016
Accepted 11 September 2016
Available online 14 October 2016

Keywords:
Carboxymethyl xanthan
gum-graft-polyacrylamide
Cross-linker
Wet granulation

ABSTRACT

The effect of Ca^{2+} ion cross-linker on acryalamide grafted carboxymethyl xanthan gum (CMXG-g-PAAm) on the drug release was investigated. Previously, CMXG was synthesized from XG and further grafted to CMXG-g-PAAm to retard the drug release. Once the $CaCl_2$ solution is added to CMXG-g-PAAm, Ca^{2+} considerably affected the drug release mechanism mainly by diffusion and erosion. In order to validate the grafted polymer, tablets were prepared using wet granulation and dry granulation methods It has been noticed that the tablets prepared by wet granulation successfully controls the release of the drug over an extended period of time. Moreover, the release profile was aligned to Korsmeyer–Peppas equation and exhibited the drug transport mechanism via diffusion and erosion.

1. Introduction

Xanthan gum (XG) is natural polysaccharide of high molecular weight obtained by a process of fermentation. The bacterium *Xanthomonas compestris* found on cabbage plants was first discovered by the United States Department of Agriculture in the year 1961, which can be able to produce an extracellular polysaccharide with excellent rheological properties. XG is the most important microbial polysaccharide available commercially [1,2]. As suspending and emulsifying agent, XG has been widely used in many cosmetic, pharmaceuticals and food products [3]. Due to its less solubility in polar solvents, the applications of the XG are limited. Generally, hydration causes swelling of XG particles that triggers the formation of gelatinous layer on the outer surface of the XG. Further, formed gelatinous layer creates hindrance to penetration of water, which, in turn, reduces the solubility of the XG [4,5]. Moreover, XG has earlier been employed to prepare sustained release matrix tablets due to its slow dissolution characteristics [6,7]. Thus, to increase the release rate, XG is modified into caboxymethyl xanthan gum (CMXG) matrixes as earlier reported by Ahuja et al. [8] and Badwaik et al. [4]; But in our investigation we found that XG matrix released nearly 50% of the drug within 16 h. Whereas, CMXG released 100% of the drug within 3 h. However, grafting of carboxymethylated gum significantly prolongs the drug release. Accordingly, we have synthesized CMXG-g-PAAm by conventional graft copolymerizationof CMXG with acrylamide [9]. We have noticed the apparent viscosity of CMXG-g-PAAm is lower than that of the CMXG, which may not be suitable to tailor the release beyond 3 h.

Cross-linking is a suitable procedure to control hydrophilicity of gums and to regulate drug release. Moreover, the bioactive substances present in the matrixes results in unwanted reactions with the chemical cross-linking agents. Especially from biomedical aspects, these will impair the biocompatibility and endow the matrix with risk in both short and long-term applications. Such adverse effects can be avoided using ionic cross-linking method. Ionic cross-linking is simple and mild procedure, thus from the aspect of safety by regulatory agencies it is more acceptable in contrast to other cross-linking methods [10].

In the same series, calcium cross-linked pectin [11,12] and alginate [13] matrices have been investigated for drug release behavior. Recently, effect of Ca^{2+} on drug release from CMXG matrix has been reported [14] to retard the release of drug. However, to date, no study has reported the drug release behavior and stability study of Ca^{2+} cross-linked CMXG-g-PAAm matrix.

In this study, we prepared CMXG-g-PAAm matrix tablets by direct compression and wet granulation (with and without use of ionic cross-linker) method. To evaluate *in-vitro* drug release profile

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http://dx.doi.org/10.1016/j.ijbiomac.2016.09.096
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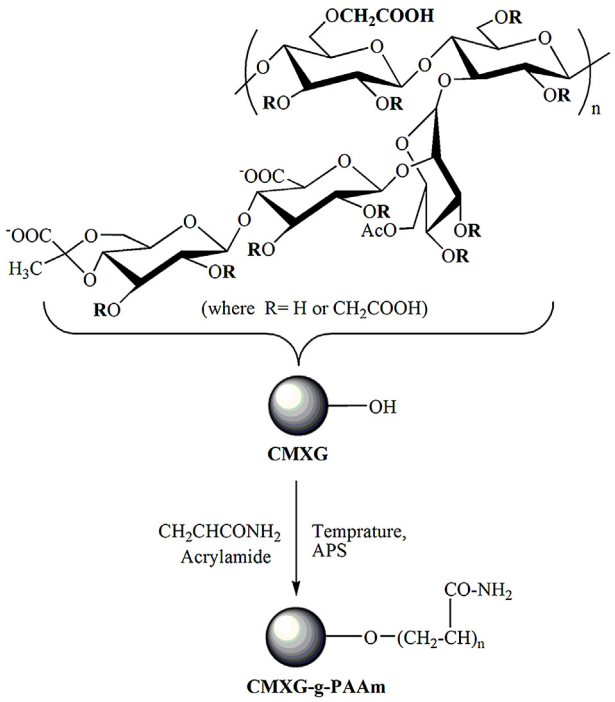

Fig. 1. Schematic representation of graft co-polymerization of acrylamide on to carboxymethyl xanthan gum.

by CMXG-g-PAAm matrix, a highly water soluble drug diltiazem hydrochloride (DTZ) was used as a model drug. DTZ is widely used for the treatment of cardiovascular disorders like arrhythmias, angina pectoris and hypertension [15,16]. Further, to confirm the safety of the grafted copolymers, toxicity studies were conducted thereof.

2. Experimental section

2.1. Materials

Xanthan gum (XG), acrylamide (AAm) and ammonium persulphate (APS) were purchased from Loba Chemie, Mumbai, India. The method of preparation and purification as well as the measurement of degree of substitution (DS) of CMXG was followed as described earlier [17]. The DS was found to be 0.87. Diltiazem Hydrochloride (DTZ) was kindly provided by ZIM Laboratories, Nagpur, India. All other chemicals used were of reagent grade, and were used as received. Nitrogen gas was purified by passing through fresh pyrogallol solution.

2.2. Synthesis of poly(acrylamide)-grafted-carboxymethyl xanthan gum (CMXG-g-PAAm)

To initiate the synthesis, APS was used under nitrogen atmosphere to produce CMXG-g-PAAm (Fig. 1) using free radical polymerization method. For this reaction, amount of CMXG (DS = 0.87) of 16 g dm^{-3}, dry basis was taken and dissolved in distil water under stirring with continuous streaming of nitrogen bubble for 1 h (75 °C). To this solution, freshly prepared aqueous solution of APS (20×10^{-4} mol dm^{-3}) and AAm (1 mol dm^{-3}) were added slowly. The reaction was observed for 75 min. The reaction mixture was cooled to ambient temperature and then poured into excess of methanol. The copolymers were then separated and dried thereof. The resulting copolymer was repeatedly washed with 30% v/v methanol until unreacted monomer and homo polymers were removed. Finally, copolymer was dried (at 50 °C) to a constant weight and kept in desiccators.

2.3. Acute toxicity study of grafted copolymer

According to the Organization of Economic Co-operation and Development guideline for the test of chemicals (OECD) guidelines, oral toxicity of CMXG-g-PAAm was carried out to ensure the safety profile of the polymer. As per the protocol, ten week old six female wister rats (non pregnant) weighing 150–200 g were selected. The Institutional Animal Ethics Committee of Rungta College of Pharmaceutical Sciences and Research, Bhilai, India has approved the experimental protocols (1189/PO/a/08/CPCSEA). All the animals were kept in chaw food and under standard laboratory conditions (22 °C temperature and in 30–70% humidity for 15 days).

Overnight fasted rats were administered with a single dose of 10 ml/kg solution via oral gavage. The animals were monitored for any behavioral change and mortality for 14 days. After the completion of the study, all the animals were sacrificed under CO_2 and examined by necropsy.

2.4. Preformulation study

2.4.1. Drug–polymer compatibility by FT-IR spectroscopy

A drug-polymer compatibility was analyzed using Fourier Transform Infrared spectrophotometer (Varian 640-IR, USA).The spectra were taken in the wave number region 4000–400 cm^{-1} as KBr pellets of drug (DTZ), polymer (CMXG-g-PAAm) and matrix formulations (F3 and F5).

2.4.2. Drug–polymer compatibility study by DSC

A differential scanning calorimetry (DSC) (Pyris Diamond TG/DTA, Singapore) was used to study the thermal analysis of drug-polymer compatibility. The drug (DTZ), polymer (CMXG-g-PAAm) and matrix formulations (F3 and F5) were scanned in the temperature range of 30–400 °C under a nitrogen atmosphere (150 ml/min). The heating rate was maintained at 10 °C/min and the obtained thermograms were observed for any type of interaction.

2.5. Preparation of matrix tablets

2.5.1. Direct compression

Matrix tablets of model drug (DTZ) were prepared employing CMXG and CMXG-g-PAAm as per the earlier reported procedure [4,8]. The equal ratio of DTZ and CMXG/CMXG-g-PAAm were mixed with 1.0% magnesium stearate in each tablet. The blended powder was directly compressed in a four station rotary tableting machine (LAB PRESS-1, Shakti Pharmatech PVT. LTD., Ahmedabad, India) using 8 mm biconvex punches and dies.

2.5.2. Wet granulation

$CaCl_2$ (0–50.00%, w/w of polymer) containing matrix tablets of CMXG-g-PAAm were prepared using wet granulation method reported earlier [14]. A damp cohesive mass of polymer was obtained with varying amount of $CaCl_2$ solution. The damp mass was then passed through #18 BS screen to form granules. These granules were dried at 60 °C and again passed through #22 BS screen. Magnesium stearate (1%) was then added to granules followed by compression in rotary press. In a similar way tablets containing DTZ (49.67%, w/w of total tablet weight) were also prepared.

2.6. Evaluation of tablets

DTZ matrix tablets were evaluated for thickness, diameter, hardness, weight variation, content uniformity and friability. The