International Journal of Biological Macromolecules 103 (2017) 347–354

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Development of smart hydrogels of etherified gum ghatti for sustained oral delivery of ropinirole hydrochloride

Somasree Ray*, Goutam Roy, Sabyasachi Maiti, Uttam Kumar Bhattacharyya, Ayantika Sil, Ritwika Mitra

Gupta College of Technological Sciences, Ashram More, G.T. Road, Asansol 713301, West Bengal, India

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 29 March 2017
Accepted 14 April 2017
Available online 27 April 2017

Keywords:
Gum ghatti
Etherification
Sodium carboxymethyl gum ghatti
Drug release

ABSTRACT

Gum Ghatti (GG) is a water soluble complex polysaccharide obtained from *Anogeissus latifolia*. Due to its non toxic and excellent emulsifying characteristics, it was widely used in different pharmaceutical preparations. Currently another facet was explored for its utility as release retardant polymer in oral controlled drug delivery system. As GG solely was incapable of forming microspheres therefore modification of GG to Sodium carboxymethyl (NaCMGG) derivative was done by carboxymethylation process and its gel forming capacity was explored by the use of trivalent cation (Aluminium chloride) which results into complete microbead system in a complete aqueous environment for controlled delivery of Ropinirole Hydrochloride (RHCl). Rheological property of NaCMGG showed pseudoplastic shear thinning behavior. Spherical shape of bead was observed under scanning electron microscope. Depending upon the formulation variables, Drug entrapment efficiency (DEE) varies from 47.66 ± 3.51 % to 71.4 ± 2.65%., and 80 to 90% drug was released in 6 h in pH 6.8 phosphate buffer. Drug release was governed by both fickian diffusion and polymer relaxation simultaneously. Compatible environment for drug entrapment was established by Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). Thus the modified derivative NaCMGG could be a promising polymer in biomedical application.

1. Introduction

Gum ghatti (GG) or Indian gum is complex polysaccharides, obtained from the species *Anogeissus latifolia* (combretaceae, Myrtales). Regularity status of USA considered GG as safe material in food additives depending on its toxicity, mutagenicity and teratogenicity. It was also used as additives in different pharmaceutical preparations like chewing gums, creams, oil and aqueous emulsions and syrups [1,2] and was marked as safe additives by the Bureau of Indian Standards, India, under Indian Standard IS 7239:1974. It is an unique polysaccharide with excellent emulsifying property [3–5] and sometimes shows better emulsifying property compared to other gum such as Gum Arabic [6]. Excellent emulsification properties of GG have evoked an interest among researchers to formulate sustained release drug delivery system using GG as rate controlling polymer.

Previously, we have seen that natural polysaccharides play an important role in the field of drug delivery system because of their non toxic nature, biocompatibility and easy amenability of chemical modification [7,8]. These biopolymers can be used to form hydrogel beads [9], nano composite hydrogels [10], pH responsive microspheres [11]. Application of hydrogels were not only restricted to the field of drug delivery and chitosan crosslinked poly(alginic) acid were used as an effective adsorbent for the removal of chromium ion from aqueous solution [12]. In this context different natural polymers like sodium alginate [13,14], gellan gum [15,16], xanthan gum [17] has been investigated for their ability to form hydrogel beads in the presence of divalent or trivalent metals ions. Sometimes some crosslinking agents like glutaraldehyde [18], positively charged amines like poly-L-lysine [19], polyethethylene imine [20], Chitosan were also added along with the natural polymers to prevent rapid release of drug from the microparticles. But the results were not encouraging. Rapid drug release from chitosan and sodium tri-polyphosphate crosslinked beads was also observed in acidic dissolution media [21]. Similar higher drug release profile in dissolution media of pH 7.4 than in acidic medium (pH 1.4) was noticed from microparticles containing phosphorylated chitosan beads with polyanion tripolyphosphate [22]. Though sodium alginate beads do not swell in acidic fluid, quick release of drug in simulated intestinal fluid within small period of time was observed [23,24] which is the main problem associated with sodium alginate. So every natural polymer has its

* Corresponding author.
E-mail address: somasreeray@yahoo.co.in (S. Ray).

http://dx.doi.org/10.1016/j.ijbiomac.2017.04.059
0141-8130/

own drawbacks and none of them seems perfectly suitable for the development of the sustained release drug delivery system. Hence there is a need to search for other natural polymers to overcome the draw backs of the existing polymers. As a part of our ongoing research program on the modification of new natural polymer for the development of sustained release preparation, we herein concentrated our knowledge on the development of microparticles using gum ghatti (GG).

RHCl is used in the treatment of Parkinson's disease and restless legs syndrome. IUPAC name of RHCl is 4-[2-(dipropyl amino) ethyl]-1,-3-di hydro-2H indol-2-one. It acts as D_2, D_3, D_4 dopamine receptor agonist with highest affinity for D_2 and metabolized by cytochrome P450.CYP1A2 enzyme. Plasma half life of RHCl is 5–6 h and it was taken as a model drug in the preparation of sustained release microparticles containing GG.

To encourage investigation in the field of natural polymer, we have made an attempt to explore the utility of GG in the field of sustained release drug delivery system. Literature survey revealed that though structural and functional property of GG has been investigated in detail, little attention has been paid on pharmaceutical applications of GG. Kaith et al. developed hydrogel system of acrylamide and acrylonitrile with GG using ascorbic acid and potassium persulphate redox pair as an initiator and N,N′-methylene-bis-acrylamide as crosslinker via free radical mechanism [25]. In another study, Kaith et al. prepared pH and electrical stimulus sensitive hydrogel using same redox pair initiator and cross linking agent [26]. However there was no report available in the literature on the development of microparticulate system using GG and modified GG in an ecofriendly, organic solvent free condition. In the present investigation GG was modified to sodium carboxymethyl gum ghatti (NaCMGG) by carboxy methylation method to improve the physicochemical properties like hydrophilicity, rheology, gel forming behavior. The degree of o-carboxymethyl substitution was also measured. Then modified gum was used to develop microparticulate system for the delivery of RHCl.

In this paper we will give an overview on the efficacy of GG or its modified form, as a potential matrix for sustained drug release of bioactive molecules. In particular, the presentation was divided in two portions. First GG was modified to NaCMGG by carboxymethylation process and then modified gum is used to develop sustained release microparticulate preparation. In this study, we have prepared Al^{3+} ion crosslinked hydrogel network beads of NaCMGG by ionotropic gelation technique and special emphasis was given on drug entrapment efficiency, in vitro drug release profile, drug polymer interaction and thus respective evaluation was done. The physical state of drug in microparticles was examined by DSC. By studying its rheological property and gel forming behavior, it was possible to establish the utility of GG in controlled release drug delivery system.

2. Material and methods

2.1. Materials

GG was purchased from Himedia Laboratories (Mumbai, India). Sodium hydroxide and ethanol were of analytical reagent grade. Analytical grade monochloro acetic acid was obtained from Thermo Fisher Scientific India Pvt. Ltd. and Merck Specialties Pvt. Ltd. (Mumbai, India) respectively. RHCl was used as a drug sample. Double distilled water was used throughout the work.

2.2. Synthesis of sodium carboxymethyl gum ghatti

For the modification of GG, initially a known amount of GG, 500 mg was taken and mixed thoroughly with a small amount of water with the help of magnetic stirrer for 1 h. For the preparation of NaOH solution (55.59% w/v), weighed amount (5.559 g) of NaOH was taken in 10 mL of water and it was stored in refrigerator. 5 mL of monochloroacetic acid was prepared by dissolving 2.259 g of monochloroacetic acid in 5 mL of water. Then previously prepared GG solution was initially treated with the previously prepared ice cold NaOH solution (2.72 mL) and stirred with glass rod for 1 h. After that, 1.36 mL of monochloroacetic acid solution was added and similarly stirred with glass rod for 1 h. During mixing, temperature was maintained at 15 °C. After proper mixing, the solution was kept in water bath at 65 °C for 1 h. Then methanol was added to the mixture and the pH was adjusted to neutrality. The precipitated gum was separated out and dried at 50 °C for further study.

2.3. Acute oral toxicity study

Acute oral toxicity study of NaCMGG was performed as per the "Organization of the Economic co-operation and development" (OECD) guideline for the test of chemicals" 425, adopted "17 December 2001". Institutional animal ethics committee (955/RO/a/2006/CPCSEA) approved the protocol of the study. Five swiss albino mice were taken for the study and they were kept in cage at 20–25 °C, 40–70% relative humidity and normal day, night photo cycle. Initially one animal was fed with NaCMGG (2 g/kg body weight) in viscous liquid condition by gavages and were kept under continuous observation up to 24 h. If the animal dies, the main test was conducted to determine LD_{50}. If the animal survives, dose four additional animals sequentially so that a total of five animals were tested. LD_{50} is greater than 2000 mg/kg if three or more animals survive. The study was continued for one month for the detection of any mortality and abnormal behavior.

2.4. Determination of degree of substitution

Weighed amount (500 g) of previously prepared NaCMGG was taken, and dispersed in 5 mL 80% v/v methanol solution. To it, excess amount of concentrated HCl was added and continuous stirring was done for 2–3 h. After proper mixing again 2–3 drops of methanol was added to the above mixture and precipitate was filtered out through Whatmann filter paper. The left over residue was washed with 80% v/v 5 mL methanol until neutrality was obtained. The residue was dried to constant weight.

Then in arleynmeyer flask, 1.5 mL 70% v/v methanol and 200 mg of dried modified gum was taken and allowed to stand for few minutes without any disturbances. To the above solution 0.5(N) 5 mL NaOH and 20 mL of distilled water was added. To dissolve the sample it was continuously stirred for 3–4 h. Then back titration was done with 0.4(N) HCl using phenolopthalein as an indicator. It was titrated up to phenolopthalein end point. Degree of substitution was measured using the following equation

$$\text{D.S.} = 0.162A(1 - 0.058A)$$

A – milliequivalent of NaOH per gram of sample.

2.5. Rheological characterisation

NaCMGG was dispersed in water and its flow characteristics with respect to spindle speed was analyzed by 'Power Law' expression,

$$t_w = k\gamma^n$$

where, t_w and γ represents shear stress and shear rate respectively, and k and n correspond to consistency and power law index. If $n = 1$, it represents Newtonian flow, if $n < 1$ represents shear thin-