International Journal of Biological Macromolecules 102 (2017) 878–884

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Chitosan — Locust bean gum interpenetrating polymeric network nanocomposites for delivery of aceclofenac

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ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 7 April 2017
Accepted 25 April 2017
Available online 26 April 2017

Keywords:
Chitosan
Locust bean gum
Nanocomposites
Interpenetrating network
Drug delivery

ABSTRACT

In this study, aceclofenac-loaded IPN nanocomposites were developed based on natural polysaccharides namely chitosan (CS) and locust bean gum (LBG) using glutaraldehyde as cross-linker. Infrared spectroscopy analysis confirmed the formation of composite materials and ensured the chemical compatibility between drug and polymers. The effect of component polymers on the drug entrapment efficiency (DEE) and particle size of the composites was examined. Increasing LBG content actually decreased the DEE from 72% to 40% and produced larger particles of 372–485 nm dimensions. However, an opposite trend was noted as the concentration of CS was increased. Out of these composites, the maximum drug entrapment efficiency of 78.92% and smallest composites of 318 nm-size was obtained at LBG: CS mass ratio of 1:5. However, CS: LBG (1:5) provided the slowest drug release profiles in phosphate buffer solution (pH 6.8) up to 8 h. The drug release data corroborated well with the swelling properties of the nanocomposites. The composite systems efficiently suppressed the burst release of drug in acidic medium (pH 1.2). The drug delivery from the nanocomposites occurred via anomalous transport mechanism in vitro. Overall, this novel chitosan- and LBG-based nanocomposites system could minimize the gastrointestinal side effects of the drug by providing medication in a slow sustained fashion.

1. Introduction

In last few years, a great deal of attention has been paid to the design of interpenetrating polymeric networking (IPN) systems for controlled drug delivery application. IPN is considered as dual polymeric composite, where at least one polymer network is synthesized or cross-linked independently in the immediate presence of the others [1]. Usually, IPN system is preferred over polymer blends because of their improved mechanical strength and ability to prevent the burst, uncontrolled swelling of polymer blends that ultimately controls the release of drug. Therefore, IPN-based drug delivery system appears to be a new avenue in drug delivery research for obtaining sustained drug release profiles [2,3]. Different biopolymer-based IPNs such as gellan gum-polyvinyl alcohol (PVA) [4], xanthan gum-PVA [5], locust bean gum-PVA [6], PVA-guar gum [7], chitosan (CS)-TSP [8], chitosan-hydroxyethyl cellulose [9], CS-methyl cellulose [10], CS-gelatin [11] have been reported for the delivery of different kind of drugs. CS, a cationic polysaccharide obtained by deacetylation of chitin have been extensively studied for developing IPN composites exclusively in conjunction with synthetic polymers such as *N,N′*-dimethylacrylamide [12], poly(*N*-isopropyl acrylamide-co-vinyl pyrrolidone) [13] due to its non-toxic, biodegradable, biocompatible nature [14]. Even, combinations of modified CS and synthetic polymers such as poly (*N*-isopropylacrylamide) [15], poly (methacrylic acid) [16] have been reported. However, the IPN systems of CS with other biopolymers are very uncommon.

CS is composed of α-1, 4-linked 2-amino-2-deoxy- α-D-glucose (*N*-acetyl glucosamine). According to United States Food and Drug Administration (USFDA), it is GRAS (Generally Recognized as Safe) material and hence, finds wide application in pharmaceutical as well as biomedical fields including drug delivery, food technology and tissue engineering [17]. Due to its fast dissolution in gastric fluid, its use is limited as oral sustained drug release carriers [18]. Considering the importance and convenience of oral route, the drug delivery properties of chitosan carriers was modified with the use of other polymer in combination. The drug substance having short biological half-life often requires frequent dosing, which ultimately may lead to toxicity due to accumulation of drug dose [19].

Locust bean gum (LBG) is a natural galactomannan extracted from the seeds of the carob tree (*C. siliqua*), and composed of α (1,4)-linked β-D- mannopyranose backbone with linked to (1,6) α-D-galactose [20]. The non-toxic LBG can be used to monitor the release of drug from its delivery carriers [21,22]. Recently, the

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http://dx.doi.org/10.1016/j.ijbiomac.2017.04.097
0141-8130/

research scientists are trying to develop biopolymer-based green composites for drug delivery. The green composites are very important due to their simple fabrication methods and low cost [23]. The components are judiciously selected to obtain a green composite system with favorable drug delivery properties, non-attainable by any of the constituents alone [24]. In composites, two or more chemically and physically different phases remain separated by a distinct interface [25,26]. However, chitosan-locust bean gum (LBG) IPN nano-composites are not reported till date.

Aceclofenac (AC) is chemically 2-[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxyacetic acid and is a non-steroidal anti-inflammatory drug with a short biological half-life of 4 h [27,28]. It is used in the treatment of osteoarthritis, arthritis, rheumatoid arthritis and ankylosing spondylitis [29]. The long-term use of conventional AC formulation is associated with various side effects such as ulcer, gastric irritation and bleeding, abdominal pain, nausea, and flatulence [30]. To overcome these drawbacks, prolonged release CS-LBG IPN nano-composites were developed for AC and characterized in vitro.

2. Materials and methods

2.1. Materials

Chitosan (deacetylation 85%) was obtained from Everest Edward, Kochi, India. Locust bean gum (LBG) (Purity 91.8%; ~M/G = 4:1; Protein ≤7%) was purchased from Hi Media Laboratories Pvt. Ltd., Mumbai, India. Aceclofenac (AC) was obtained as a gift sample from Cipla Pharmaceutical Pvt. Ltd., Sikkim, India. Glutaraldehyde (GA, 25% v/v) was purchased from Merck specialties Pvt. Ltd., Mumbai, India. All other reagents and chemicals were of analytical grade.

2.2. Preparation of AC-loaded CS-LBG IPN nano-composites

Chitosan was first dissolved in 10 ml 1% (v/v) glacial acetic acid solution and added to this; an aqueous LBG dispersion was added. Then pre-weighed aceclofenac (100 mg) was mixed with the polymer blend under continuous magnetic agitation (Remi Equipment Pvt. Ltd., Mumbai, India) until homogeneous drug dispersion was formed. The pH of blended dispersion was adjusted to pH 5.4 using 0.2 M sodium hydroxide (NaOH) solution. Then, 1 ml GA was added to the dispersion and continuously stirred for 1 h. The prepared cross-linked polymer composites were centrifuged at 6000 rpm for 30 min. The drug-loaded IPN nano-composites were washed with glycine-water mixture to remove non-reacted GA. The orange color of the washings disappeared; the final washings were heated with a deep-blue alkaline Fehling's solution. No brick-red precipitate (a negative test) was formed, thus confirming removal of residual GA in the washings [31]. Finally, the drug-loaded nano-composites were stored at −20 °C overnight and lyophilized (Eyela FDU-1200, Japan). The dried samples were stored in desiccators for further use. The composition of different nanocomposite systems is shown in Table 1.

2.3. Fourier transform-infrared (FTIR) spectroscopy

The IR spectral data of AC, CS, LBG, and AC-loaded IPN nano-composites were obtained after scanning of KBr pellets with powder samples using Perkin Elmer FTIR spectrophotometer (Spectrum RX1, USA) in the wave number range 4000–400 cm^{-1} at a resolution of 4 cm^{-1} with scan speed of 2 mm/sec.

Table 1
Composition of chitosan-locust bean gum nanocomposites containing aceclofenac.

IPN composites	Polymers (mass ratio) CS:LBG	Polymers		AC (mg)	GA (ml)
		CS (mg)	LBG (mg)		
CSLBG-1	1:5	50	250	100	1
CSLBG-2	1:2	100	200	100	1
CSLBG-3	1:1	150	150	100	1
CSLBG-4	2:1	200	100	100	1
CSLBG-5	5:1	250	50	100	1
CSLBG-6	3:0	300	–	100	1

2.4. Measurements of particle size & zeta potential

The mean size and zeta potential of the nano-composites were measured by Zetasizer nano ZS90 (Malvern Instruments, UK) at a detector angle of 90° at a temperature of 25.2 °C. The samples were prepared by dilution in deionized water at appropriate concentration. Each sample was measured in triplicate.

2.5. Drug entrapment efficiency (DEE) of CS-LBG IPN nano-composites

Lyophilized CS-LBG IPN nanocomposites (100 mg) were dispersed into 100 ml phosphate buffer solution (pH 6.8), kept overnight and sonicated (FS-600, Frontline Sonicator, Frontline Electronics and Machinery Pvt. Ltd., India) thereafter for 15 min for extraction of the drug. The insoluble polymeric debris was removed by filtration through Whatman® filter paper (No. 40) and the filtrate was analyzed by UV–vis spectrophotometer (Thermo Scientific, Evolution-200, UK) at 274 nm. The DEE of drug-loaded IPN nanocomposites was calculated by the following formula:

$$\text{DEE}\ (\%) = \frac{\text{actual drug present in IPN nanocomposites}}{\text{experimental drug present in IPN nanocomposites}} \times 100$$

2.6. Swelling study

The swelling of the nano-composites was examined in pH 6.8 buffer systems for 1 h. Known amount of composites was immersed in 100 ml of dissolution media and the samples were withdrawn at pre-determined intervals, blotted with tissue paper and weighed. The swelling percentage was calculated by dividing the differential weight between swollen and dry composites with the dry sample weight, followed by multiplication with 100.

2.7. In vitro drug release study

In vitro release of AC from CS-LBG IPN nano-composites was studied as follows. The drug- loaded IPN nano-composites equivalent to 100 mg aceclofenac were placed in dialysis bag (MWCO 12–14 kDa, HiMedia Laboratories Pvt. Ltd., Mumbai, India) containing 5 ml of dissolution medium (phosphate buffer, pH 6.8). Other end of the dialysis bag was tied off and immersed in 900 ml of dissolution medium (Veego VDA-6D, Veego Instruments Co-operation, Mumbai, India) containing. USP type II dissolution apparatus was maintained at 37 ± 1 °C with a paddle speed of 50 rpm. The dialysis bag acted as a donor and that of dissolution vessel as the receptor compartments. An aliquot (5 ml) was collected at predetermined time intervals, and the same volume of fresh buffer was added into dissolution vessel to maintain the sink condition throughout the experiment. The aliquots were then filtered with Whatman® fil-