International Journal of Biological Macromolecules 72 (2015) 47–53

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Metal ion-induced alginate–locust bean gum IPN microspheres for sustained oral delivery of aceclofenac

Sougata Jana*, Arijit Gandhi, Subrata Sheet, Kalyan Kumar Sen

Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol 713301, W.B., India

ARTICLE INFO

Article history:
Received 5 June 2014
Received in revised form 25 July 2014
Accepted 31 July 2014
Available online 9 August 2014

Keywords:
Alginate
Locust bean gum
Microspheres
Sustained drug delivery
Anti-inflammatory activity

ABSTRACT

The alginate microspheres represent a useful tool for sustained oral delivery of drugs but exhibit several problems associated with the stability and rapid release of drugs at higher pH values. To overcome these drawbacks, alginate–locust bean gum (LBG) interpenetrating microspheres were prepared by calcium ion (Ca^{+2}) induced ionotropic gelation technique for prolonged release of aceclofenac. The drug entrapment efficiency of these microspheres was found to be 59–93%. The microspheres lied in the size range of 406–684 μm. Scanning electron microscopy revealed spherical shape of the microspheres. No drug–polymer interaction was evident after infrared spectroscopy analysis. The microspheres provided sustained release of aceclofenac in phosphate buffer solution (pH 6.8) over a period of 8 h. The drug release data were fitted into the Korsmeyer–Peppas model and the drug release was found to follow anomalous (non-Fickian) diffusion mechanism. Pharmacodynamic study of the microspheres showed a prolonged anti-inflammatory activity in carrageenan-induced rat paw model following oral administration.

1. Introduction

Microspheres refer to the micro-particulate polymer-based carrier systems for drug delivery applications. They offer advantages such as limited fluctuation of drug–plasma profile within a therapeutic range, reduction in side effects, decreased dosing frequency and improved patient compliance [1,2]. Over the past few decades, several research papers have been published on microspheres, composed of naturally occurring biodegradable polymers [3]. Among naturally occurring biodegradable polymers, sodium alginate and locust bean gum (LBG) are widely used polymer candidates for the designing and development of various drug delivery systems. Sodium alginate, a linear anionic polysaccharide obtained from brown algae is known to biodegradable and non-toxic [4]. Sodium alginate, the sodium salt of alginic acid, belongs to a family of linear copolymer composed of two monomeric units, β-D-mannuronic acid residue, α-L-guluronic acid residue and regions of interspersed both the residues [5,6]. Alginates have been used as matrix forming material in the design of various drug delivery systems to achieve sustained drug release over a prolonged period due to its hydro-gel forming properties [7]. On the other hand, locust bean gum is also derived from the endosperm of the seeds of *Ceretonia siliqua* Linn belonging to the family Fabaceae [8]. Locust bean gum has a wide potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. It can be tailored made to suit the demands of applicants in both the pharmaceutical and biomedical areas. This group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as a conventional excipient and more specifically as a tool in polymeric controlled drug delivery. It consists mainly of a neutral galactomanan polymer made up of 1, 4-linked D-mannopyronosyl units and every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit [9].

Sodium alginate have ability to undergo ionotropic gelation in aqueous solution in presence of multivalent cations like Ca^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Al^{3+}, etc. [10]. On the other hand, LBG also able to undergo ionotropic gelation in aqueous solution in presence of cations like Al^{3+} [11,12]. The mechanical stability of the ionotropically cross-linked gel systems is provided by multivalent cations. In literatures, the combination of alginate and LBG as drug delivery carrier was not found. Though drug loaded alginate microspheres represent a useful tool for sustained oral drug delivery but show several problems, mainly related to the stability, and rapid drug release at higher pH values. To overcome these drawbacks, the present investigation was undertaken to design IPN microspheres using a dual combination of alginate and LBG for sustained drug delivery.

Aceclofenac is chemically 2-[(2′,6′-dichlorophenyl) amino] phenylacetoxyacetic acid, as a non-steroidal anti-inflammatory drug (NSAID) with short half-life (4 h) indicated for the symptomatic treatment of pain and inflammation [13]. It is also used in

* Corresponding author. Tel.: +91 9434896683.
E-mail address: janapharmacy@rediffmail.com (S. Jana).

http://dx.doi.org/10.1016/j.ijbiomac.2014.07.054
0141-8130/

Table 1
The percentage of polymers, drug (aceclofenac) and cross-linker for the preparation of different aceclofenac-loaded microspheres.

Formulation code	Sodium alginate (% w/v)	LBG (% w/v)	Aceclofenac (% w/v)	$CaCl_2$ (% w/v)
F1	1	1	1	2
F2	1	1	1	4
F3	1	2	1	2
F4	1	2	1	4
F5	1	3	1	2
F6	1	3	1	4
F7	2	1	1	2
F8	2	1	1	4
F9	3	1	1	2
F10	3	1	1	4
F11	2	2	1	2
F12	2	2	1	4

the treatment of arthritis, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [14]. Aceclofenac is reported to produce side effects like gastric irritation, ulcer, particularly diarrhoea, nausea, abdominal pain and flatulence, *etc.* as result of prolong treatment [15,16]. Due to its short half-life, its recommended dose is considered as 200 mg daily in divided doses. To reduce dosing frequency and adverse effects during prolong treatment, sustained release dosage of aceclofenac to deliver aceclofenac at a slow release rate over an extended period of time is essential. Therefore, aceclofenac was used as model drug in this investigation.

2. Materials and methods

2.1. Materials

Aceclofenac was received as a gift sample from Cipla Pharmaceuticals, India; Sodium alginate was commercially purchased from Merck Specialities Pvt. Ltd., India; LBG was procured from Hi-Media, India; Calcium chloride was purchased from S.D. Fine chemicals Ltd, India; all other reagents and chemicals used in this study were of analytical grade.

2.2. Preparation of microspheres

The aceclofenac-loaded microspheres made of alginate–LBG were prepared through interfacial ionotropic gelation technique. Briefly, required amounts of sodium alginate and LBG were dissolved in deionized water (100 ml) using magnetic stirring of 300 rpm for 30 min separately. Both the polymer solution was mixed with continuous magnetic stirring of 300 rpm for 30 min again. Afterwards, aceclofenac was added to the mixture gels of sodium alginate and LBG. Aceclofenac containing polymeric gels were stirred using magnetic stirring of 300 rpm until they became bubble free. The prepared homogeneous bubble-free drug-polymeric solutions were extruded drop wise into counter-ion solutions using a 25 ml hypodermic syringe (1 mm diameter) with constant stirring. The counter-ion solutions contain different concentrations of calcium chloride. Added droplets were retained in the counter-ion solutions for 5 min to complete the curing reaction and to produce rigid microspheres. The wet microspheres were collected by decantation, and washed two times with distilled water and dried in room temperature for overnight. The dried microspheres containing aceclofenac were stored in a desiccator until used. Different microsphere formulations along with percentage of polymers, drug (aceclofenac) and cross-linker are enlisted in Table 1.

2.3. Determination of percentage yield

The total amount of microspheres for each formulation batch was obtained by weighing these prepared microspheres in a weighing balance (Dhona 160 D, Dhona Instrument Pvt. Ltd., India.) and the theoretical weight was calculated by taking into consideration the weight of the drug and polymer employed during the preparation of microspheres. The percentage yields of these microspheres were calculated using this following formula:

$$\text{Percentage yield} = (\text{Weight of microspheres recovered} / \text{Total weight of drug and polymers}) \times 100$$

2.4. Estimation of drug entrapment efficiency

Accurately weighed 100 mg of prepared aceclofenac-loaded microspheres from each batch were taken separately and were placed in 500 ml of phosphate buffer, pH 6.8, and kept it overnight followed by sonication for 15 min in a sonicator (Frontline sonicator, FS-600, Frontline electronics and machinery Pvt. Ltd., India). The polymer debris formed after disintegration of beads was removed filtering through Whatman® filter paper (No.40). The drug content in the filtrate was determined using a UV–vis spectrophotometer (Shimadzu, Japan) by measuring absorbance at λ_{max} of 274 nm. The drug entrapment efficiency of microspheres was calculated using this following formula:

$$\text{Drug entrapment efficiency}(\%) = (\text{Actual drug content in microspheres} / \text{Theoretical drug content in microspheres}) \times 100$$

2.5. Particle size determination

The size of the prepared microspheres was measured by using digital slide callipers (CD-6 CS, Mitutoyo Corporation, Japan). Hundred particles were taken and inserted in between the space of two metallic plates. Diameters of resultant particles were displayed in the digital screen of the previously calibrated equipment.

2.6. Surface morphology analysis

The surface morphology of this formulated microsphere was analyzed by scanning electron microscope (SEM) (JEOL, JSM-6360, Japan). Microsphere were gold coated by mounted on a brass stub using double-sided adhesive tape and under vacuum in an ion sputter with a thin layer of gold (3–5 nm) for 75 s and at 15 kV to make them electrically conductive and their morphology was examined.

2.7. Swelling behaviour measurement

Swelling behaviour measurements of prepared microspheres were carried out in 0.1 N HCL (pH 1.2) and phosphate buffer of pH 6.8. 100 mg microspheres were placed in vessels of dissolution apparatus (Campbell Electronics, India) containing 500 ml respective media. The experiment was carried out at $37 \pm 1\,^{\circ}C$ under 50 rpm paddle speed. The swelled microspheres were removed at predetermined time interval and weighed after drying the surface by using tissue paper. Swelling index was determined using the following formula:

$$\text{Swelling index} = [(\text{Weight of microspheres after swelling} - \text{Dry weight of microspheres}) / \text{Dry weight of beads}] \times 100$$