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Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method

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ABSTRACT

The parameters influencing alginate ionotropic gelation and the production of alginate beads loaded with hydrosoluble ibuprofen lysine salt (IBU-L) were studied, as well as the optimization of the method for its attainment. A three-factor and three-level factorial design (3^3) was carried out to determine the influence of three experimental variables: polymer concentration, $CaCl_2$ concentration, and curing time on the dependent variables drug load and encapsulation efficiency. The effect of the pH used in the preparation bath was also evaluated. Concentrations of $CaCl_2$ and pH of gelling bath were seen to affect bead formation and stability as well as their ability to properly entrap the drug. In this work, IBU-L was used as a model of a non-steroidal anti-inflammatory drug with good solubility in alginate solutions. IBU-L was successfully encapsulated in alginate beads obtained by the ionotropic gelation method. The obtained alginate matrixes are able to modify the release of the entrapped IBU-L and this occurs in a pH-sensitive way that can be correlated with the swelling behaviour of the alginate-produced beads. Morphological characteristics were evaluated by means of scanning electron microscopy.

1. Introduction

Biopolymers are a class of natural chemicals characterized by having repetitive structural units and a wide distribution in nature. A growing interest in these compounds has given rise to a large number of published works, not only because of their low cost, biocompatibility, biodegradability and ready availability but also because of their potential use for the attainment of drug controlled delivery systems (Coviello et al., 2007).

Sodium alginate is a particularly attractive biopolymer that has a wide range of applications in the field of biomedicine. Alginate is a linear, unbranched polysaccharide co-polymer composed of 1,4-linked β-D-mannuronic acid (M-block) and α-L-guluronic acid (G-block), which are found in varying composition and sequence (Gacesa, 1988). Although alginic acid can be produced by bacteria (Sabra et al., 2001), it is commonly extracted in large amounts from algae belonging to the family of the Phaeophycea (brown algae), its sodium salt (sodium alginate) is obtained and is a water soluble polymer (Coviello et al., 2007). Depending on the species and parts of the marine algae used the alginate composition will be determined, however, other parameters such molecular weight and salt form may be profiled in the processing (Sabra et al., 2001). The composition sequence of polymer blocks and molecular weight of alginates are important as these factors determine the physical properties of the formed gel (Haug et al., 1967).

One of the properties that makes alginate useful in biomedical applications is their ability to form strong thermostable gels achieved through the exchange of sodium ions from G-blocks with divalent cations, such as Ca^{2+}, Ba^{2+}, Sr^{2+}, Zn^{2+}, that are located in electronegative cavities, and the staking of G-blocks to form an egg-box structure (Heng et al., 2003), resulting in a thick membrane however permeable to small molecules and liquids. This property is the basis of different potential applications, such as drug delivery systems (Coviello et al., 2007), bioartificial organs (Zimmermann et al., 2005), cell immobilization (Redenbaugh et al., 1986; Visted et al., 2001), enzyme immobilization (Burns et al., 1985) and protein immobilization (Velings and Mestdagh, 1994). The ionic gelation of alginate molecules offers a flexible and easily controllable process for manipulating the characteristics of the beads which are important in controlling the drug release rate (Bodmeier and Wang, 1993; Arica et al., 2005). The formed alginate gels have pH-sensitive swelling properties which are interesting for acid sensitive drugs in order to avoid attack by gastric acids or to control the site of

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drug release. Non-steroidal anti-inflammatory drugs (NSAIDs) have been profiled as candidates where alginate gels may be potential utility (Puttipipatkhachorn et al., 2005; Hwang et al., 1995).

Ibuprofen lysine (IBU-L) is the water soluble lysine salt of ibuprofen, a propionic acid derivative with well known anti-inflammatory analgesic and antipyretic properties as well as a good benefit-risk ratio when compared with other NSAIDs (Busson, 1986; Moore, 2003). Ibuprofen lysine was developed in order to enhance the speed of absorption of ibuprofen and to minimize the time of onset of therapeutic effect (Mehlisch et al., 1995). Due to its short plasma half-life of 1–3 h following oral dosing and gastric irritation, ibuprofen is an ideal candidate for preparing prolonged or controlled release drug products. The lysine salt of ibuprofen also has a bad taste whose masking can be useful for oral formulations.

Although several works have been published using alginate to produce beads entrapping the non-soluble form of ibuprofen (Arica et al., 2005; Hwang et al., 1995; Ray et al., 2010), few works are available with soluble forms. The aim of the present study is to develop ibuprofen lysine loaded alginate beads with potential modified release properties, to investigate the influence of experimental conditions on the complex formation, as well as the optimization of the method for their preparation.

2. Materials and methods

2.1. Materials

IBU-L (Laboratorios FARDI, Barcelona); Sodium alginate (MANUGEL® DMB) was kindly donated by ISP, Spain; Calcium Chloride (FAGRON, Spain), all other reagents were of analytical grade (PANREAC, Spain).

2.2. Alginate–IBU-L solutions

Alginate solutions of 1, 2 and 3% (w/v) were prepared by dissolving sodium alginate powder in deionized water and stirring until complete dissolution. To determine the optimal drug concentration, ibuprofen lysine (IBU-L) was dissolved in the respective alginate solutions to obtain final concentrations of drug ranging from 5 to 50% (w/w). Further experiments were carried out at a fixed IBU-L concentration of 17% (w/w), equivalent to *ca.* 10% (w/w) of ibuprofen as base.

2.3. Alginate–IBU-L bead preparation

Beads were obtained by extruding through a 0.25 mm needle the different alginate – IBU-L solutions into a gelling bath containing $CaCl_2$ at 1, 2 and 4% (w/v). Curing times of 30, 60, 90 and 120 min were studied. Bead formation and behaviour in the bath were observed visually. Height from the dropping device to bath surface was controlled. Beads were left in the bath during curing time and filtered through a sieve (Ø = 0.200 mm). The obtained beads were washed with deionized water and vacuum dried at room temperature until constant weight.

2.4. Bead formation

The ability of the polymeric solution to form adequate beads was visually assessed, proper formation being considered when the generated drops gelled instantly in the bath, rendering spherical and regular beads at the bottom of the container. When drops were disintegrated as they made contact with the gelling bath and irregular shapes or floating beads were obtained on the bath surface, bead formation was considered inappropriate. Bead size was determined as the average diameter of 10 beads measured by means of a Vernier calliper with to accuracy of ±0.01 mm.

Table 1
Coded variable description and values.

	Independent variables	Units	Level values		
			Low −1	Medium 0	High 1
X_1	Polymer concentration	%	1	2	3
X_2	$CaCl_2$ concentration	%	1	2	4
X_3	Curing time	min	30	60	120

	Dependent variables	Units
Y_1	Drug load	mg/g
Y_2	Encapsulation efficiency	%

2.5. Statistical design and analysis

A full factorial experimental design was used in order to evaluate the main effects and the influence of the studied independent variables (polymer concentration, $CaCl_2$ concentration and curing time) on the observed responses (drug load and encapsulation efficiency) with the aim of further selecting the optimal values of the formulation parameters. A full factorial 3^3 design was used, consisting of 27 runs. The design was generated and analyzed using STATGRAPHICS® software (StatPoint Technologies Inc., Warrenton, VA). Table 1 depicts the independent and the dependent variables respectively. Table 2 depicts the experimental design indicating the different runs with the respective coded levels.

2.6. IBU-L load and encapsulation efficiency

To determine the IBU-L loads, 20 mg of dried beads attained in each condition were accurately weighed and quantitatively placed in a phosphate buffer (pH = 8) solution under shaking until bead disintegration. Supernatants were filtered in a 0.45 μm syringe filter (Millipore Milliflex®-HV) and spectrophotometrically analyzed

Table 2
Experimental matrix and observed responses.

Run	Coded variable level			Observed response	
	X_1	X_2	X_3	Y_1	Y_2
1	−1	−1	−1	0	0
2	−1	−1	0	0	0
3	−1	−1	1	0	0
4	−1	0	−1	0	0
5	−1	0	0	0	0
6	−1	0	1	0	0
7	−1	1	−1	949	81.12
8	−1	1	0	966	83.29
9	−1	1	1	927	84.38
10	0	−1	−1	644	73.12
11	0	−1	0	663	75.94
12	0	−1	1	652	72.52
13	0	0	−1	883	79.48
14	0	0	0	878	78.10
15	0	0	1	863	78.83
16	0	1	−1	848	80.35
17	0	1	0	840	83.62
18	0	1	1	853	81.17
19	1	−1	−1	635	67.12
20	1	−1	0	624	68.33
21	1	−1	1	648	68.01
22	1	0	−1	837	74.21
23	1	0	0	887	77.52
24	1	0	1	868	73.30
25	1	1	−1	809	73.25
26	1	1	0	847	78.30
27	1	1	1	826	71.40