Journal of Drug Delivery Science and Technology 26 (2015) 35–43

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Original research

Calcium alginate multi-unit oral dosage form for delayed release of celecoxib

Lorena Segale*, Paolo Mannina, Lorella Giovannelli, Franco Pattarino

Department of Pharmaceutical Sciences, University of Piemonte Orientale, Largo Donegani 2/3, 28100 Novara, Italy

ARTICLE INFO

Article history:
Received 8 January 2015
Received in revised form
10 February 2015
Accepted 21 February 2015
Available online 24 February 2015

Keywords:
Sodium alginate
Celecoxib
Polymeric beads
Intestinal drug release

ABSTRACT

Calcium alginate beads containing celecoxib dissolved in a self-emulsifying phase were developed and characterized with the aim of ensuring a control on the site of drug release. The influence of different variables (concentration of the cross-linking agent, hardening time and amount of loaded drug) on the physico-chemical and biopharmaceutical properties was evaluated. Microscope images showed spherical dried beads and DSC revealed the absence of drug in crystalline state. The swelling behaviour of the beads was pH-sensitive and was not significantly influenced by the different variables selected. All the formulations were able to reduce the drug release at low pH and guaranteed a complete drug release at intestinal pH. In particular, at pH 7.4 the effect of the concentration of the cross-linking agent was evident: the rate and the extent of celecoxib release decreased significantly as the cross-linking agent concentration increased.

According to the results presented in this study, adopting 15 min of hardening time in a solution of 100 mM $CaCl_2$ and high drug loading, it is possible to obtain multi-unit systems characterized by good mechanical resistance, scarce swelling and release in acidic environment and good drug availability performances in the intestinal fluids.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain and menstrual symptoms. The mechanism of action of celecoxib is the inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective non-competitive inhibitor of cyclooxygenase-2 (COX-2). Its polar sulphonamide side chain binds a hydrophilic side pocket region close to the active COX-2 binding site.

Recently, this drug has been most frequently investigated for its anticancer activity using *in vitro* and *in vivo* models [5,13,19,24]. Preclinical studies on celecoxib reported prominent anticancer activity against head and neck squamous cell carcinoma, colon cancer, breast cancer and lung cancer [5,19]. Despite the approval of oral celecoxib dosage forms by FDA (Food and Drug Administration) for the adjuvant therapy in patients with familial polyposis and precancerous disease of colon, the combination of relevant side effects (thromboembolism and cardiovascular risk) and poor water solubility limit its usage in cancer therapy [3,27,28].

Celecoxib is classified as a BCS class II drug due to its low aqueous solubility (less than 5 μg/mL) and good permeability [2,14,35]. Its low solubility determines transient and low absorption after oral administration. Numerous efforts have been made to overcome this drawback and to improve oral bioavailability of the drug [10,21]. To this purpose, celecoxib has been loaded in self-emulsifying systems, in liposomes, in microemulsions, in lipid microparticles [6,12,16,17,20,26,29,30,33,35,37].

Alginates belong to a family of unbranched polysaccharides, mainly isolated from brown algae and composed of guluronic (G) and mannuronic (M) acid residues, arranged in homopolymeric blocks (MM, GG) and also in heteropolymeric blocks (MG). The molecular axial orientation of G-blocks forms molecular 'pockets' that can be occupied by di- and trivalent ions (Ca^{2+}, Sr^{2+}, Ba^{2+}, Al^{3+}) which cross-link the polymer giving a three-dimensional network able to entrap water molecules. The alginate chains bind together forming junction zones, sequentially leading to gelling of the solution mixture. The reactivity towards di- or trivalent ions, and the subsequent gel formation, is a direct function of the average chain length of G blocks. Therefore, alginates with the highest G

* Corresponding author.
E-mail address: lorena.segale@pharm.unipmn.it (L. Segale).

http://dx.doi.org/10.1016/j.jddst.2015.02.001
1773-2247/© 2015 Elsevier B.V. All rights reserved.

fractions possess the strongest ability to form gels. When, for example, an aqueous solution of sodium alginate is added drop by drop to an aqueous solution of calcium chloride, each drop forms a gel with spherical shape.

Since the composition and block structure vary greatly for different types of alginate, it follows that both gel and ion-binding properties change according to the characteristics of the selected alginate and to the nature of the cross-linking ion [31]. Alginate beads are used in a number of pharmaceutical, biomedical and biotechnological applications [7,8,11,23] according to their many advantages. These beads are non-toxic when orally administered; they are highly biocompatible, mucoadhesive, able to protect an entrapped drug from the acidic environment of the stomach. If dried, they are able to re-swell acting as controlled release systems [36]; moreover, the mild experimental conditions for the bead preparation make these systems adequate for cell encapsulation preserving their viability [18].

Celecoxib-loaded alginate beads could represent a good performing drug delivery system able to localize and address the release of the drug, reducing the total administered dose and the side effects. In this work, the attention was focused on the development and characterization of calcium-alginate beads containing celecoxib dissolved in a self-emulsifying phase with the aim to verify their potential as drug delivery vehicle.

In detail, the physico-chemical characteristics of the beads, their swelling behaviour and their release performances were evaluated as a function of the concentration of the cross-linking divalent ions (Ca^{2+}), of the contact time of polymer with the cross-linking agent and of the amount of loaded drug.

2. Materials and methods

2.1. Materials

Celecoxib (CLX) was obtained from Chemos GmbH. Sodium alginate (SA) (molecular weight 120,000–190,000 g/mol; ratio of mannuronic-guluronic 1.56) was purchased from Sigma–Aldrich (St Louis, MO, USA). Labrasol (caprylocaproyl macrogol-8 glycerides) was kindly donated by Gattefossè (Milan, Italy); D-α-tocopheryl polyethylenglycol 1000 succinate (TPGS) was gifted from Isochem (Gennevillers, France). All other reagents were of analytical grade and used as received.

2.2. Methods

2.2.1. Preparation of celecoxib calcium alginate beads

Sodium alginate was dissolved in deionised water at a concentration of 1.5% (w/w). The gelling medium was prepared solubilising different amounts of $CaCl_2$ in deionised water in order to obtain 100, 200 and 300 mM solutions. Weighed amounts of Labrasol and TPGS were mixed together and heated to 50 °C; when TPGS was in the melted state, the drug was dissolved in the excipient solution obtaining the celecoxib-loaded self-emulsifying phase. The sodium alginate solution and the self-emulsifying phase were mixed in selected ratio (4:1) until a homogeneous emulsion was obtained. The percent composition of the investigated formulations was reported in Table 1.

The emulsion, composed of sodium alginate solution and celecoxib-loaded self-emulsifying phase, was added drop by drop to the gelation bath using a 10 mL syringe equipped with a G23 needle under constant gently stirring at room temperature. As soon as the drops entered in contact with the gelation medium, calcium ions cross-linked alginate and beads were formed. After a preselected hardening time (5, 15 or 45 min), the beads were recovered, rapidly washed with deionised water to eliminate the excess of calcium ions and then dried in an oven at 40 °C over night.

Table 1
Composition of systems submitted to the gelation process. Sodium alginate solution and self-emulsifying phase were mixed in 4:1 ratio.

Formulation	Sodium alginate (% w/w)	Self-emulsifying phase (% w/w)	$CaCl_2$ concentration (mM)	Gelation time (min)
C1	1.5	Celecoxib 27.4 Labrasol 68.5 TPGS 4.1	100	5
C2	1.5	Celecoxib 27.4 Labrasol 68.5 TPGS 4.1	100	15
C3	1.5	Celecoxib 27.4 Labrasol 68.5 TPGS 4.1	100	45
C4	1.5	Celecoxib 27.4 Labrasol 68.5 TPGS 4.1	200	15
C5	1.5	Celecoxib 27.4 Labrasol 68.5 TPGS 4.1	300	15
C6	1.5	Celecoxib 15.0 Labrasol 80.9 TPGS 4.1	100	5
C7	1.5	Celecoxib 15.0 Labrasol 80.9 TPGS 4.1	100	15
C8	1.5	Celecoxib 15.0 Labrasol 80.9 TPGS 4.1	100	45

2.2.2. Morphology and particle size

Shape and morphology of wet and dried beads were preliminary evaluated using a stereomicroscope (Motic SMZ168) equipped with a videocamera (Moticam 2500). The size of beads was determined from the stereomicroscope images using an image analysis software (Motic Images Plus 2.0); for each formulation, particle size was the average value of diameter measured on 20 dried units.

The shape factor (SF), which provided information about the roundness of particles, was calculated by the following equation:

$$SF = \frac{4\pi \times area}{perimeter^2}$$

The closer the value of the shape factor was to 1, the rounder the bead was [1].

The surface and the cross-section morphology of beads were observed by Scanning Electron Microscopy (E-SEM FEI Quanta 200) analysing the samples under low vacuum without metallization.

2.2.3. Drug content

An accurately weighed amount of each formulation was treated with phosphate buffer solution at pH 6.8 (100 mL) added of sodium lauryl sulphate (SLS, 0.75%). The mixture was stirred and heated at 70 °C for 2 h in order to guarantee the complete extraction and solubilisation of celecoxib. After cooling, the mixture was filtered (Durapore membrane filters, GVPP, 0.22 μm, Millipore) and the solution analysed with an UV/Vis spectrophotometer (Perkin Elmer Lamba 35) at 255 nm wavelength. The results are the average of three determinations.

2.2.4. Labrasol determination by gas chromatography

The study was carried out through the identification and calculation of the distribution of fatty acids by chromatography in a methyl ester gas phase after hydrolysis and methylation of the product.

Download English Version:

https://daneshyari.com/en/article/2483263

Download Persian Version:

https://daneshyari.com/article/2483263

Daneshyari.com