Journal of Pharmaceutical Sciences xxx (2016) 1-8

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Formulation and Coating of Alginate and Alginate-Hydroxypropylcellulose Pellets Containing Ranolazine

Lorena Segale [1,*], Paolo Mannina [1], Lorella Giovannelli [1], Susanne Muschert [2,3], Franco Pattarino [1]

[1] Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Novara 28100, Italy
[2] College of Pharmacy, Univ. Lille Nord de France, Lille 59006, France
[3] INSERM U 1008, Lille 59006, France

ARTICLE INFO

Article history:
Received 7 June 2016
Revised 28 July 2016
Accepted 1 August 2016

Keywords:
alginate
hydroxypropylcellulose
ranolazine
polymeric pellets
enteric coating

ABSTRACT

The formulation and the coating composition of biopolymeric pellets containing ranolazine were studied to improve their technological and biopharmaceutical properties. Eudragit L100 (EU L100) and Eudragit L30 D-55-coated alginate and alginate-hydroxypropylcellulose (HPC) pellets were prepared by ionotropic gelation using 3 concentrations of HPC (0.50%, 0.65%, and 1.00% wt/wt) and applying different percentages (5%, 10%, 20%, and 30% wt/wt) of coating material. The uncoated pellets were regular in shape and had mean diameter between 1490 and 1570 μm. The rate and the entity of the swelling process were affected by the polymeric composition: increasing the HPC concentration, the structure of the pellets became more compact and slowed down the penetration of fluids. Coated alginate-HPC formulations were able to control the drug release at neutral pH: a higher quantity of HPC in the system determined a slower release of the drug. The nature of the coating polymer and the coating level applied affected the drug release in acidic environment: EU L100 gave better performance than Eudragit L30 D-55 and the best coating level was 20%. The pellets containing 0.65% of HPC and coated with 20% EU L100 represented the best formulation, able to limit the drug release in acidic environment and to control it at pH 6.8.

Introduction

An interpenetrating polymer network (IPN) is a system that includes 2 polymeric networks not covalently bonded to each other; they cannot be separated unless the inter-network entanglements are broken.[1] IPN offers the key attributes of one of the constituting polymers while it maintains the critical attributes of the other. In some cases, the properties of the IPN could be specific for the final system and not observed in either of the 2 single networks alone.[2] When one of the two polymers is linear, a semi-IPN (sIPN) results.[3]

Many researchers are interested in IPNs considering that they could be a useful way to enhance the performance of hydrogels. They are water-swollen polymers advantageous in a variety of pharmaceutical and biomedical applications due to their biocompatibility, high water content, and, in some cases, responsiveness to stimuli[4,5]; these properties make hydrogels excellent materials as drug delivery vehicles and tissue scaffolds.

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 chains, giving a three-dimensional network able to entrap water molecules.[6,7] The formed gel has a particular structure, usually described as "egg-box." Ion cross-linked alginate has usually low mechanical stability; a strategy to improve the mechanical stability of alginate gels in aqueous media is the blending of additional polymers in the alginate solution.[8] In the preparation of IPN and sIPN, sodium alginate (SA) was combined with various polymers.[9-13] The use of ether cellulose derivatives (as hydroxypropylmethylcellulose, hydroxypropylcellulose [HPC], carboxymethylcellulose) to form sIPN systems with alginate has been investigated in pharmaceutics with the aim of obtaining controlled drug release systems.[14-18]

Declaration of interest: The authors report no declarations of interest.

* *Correspondence to:* Lorena Segale (Telephone: +39-0321-375862; Fax: +39 0321 375621).
E-mail address: lorena.segale@uniupo.it (L. Segale).

http://dx.doi.org/10.1016/j.xphs.2016.08.001
0022-3549/

Ranolazine (RNZ) is a novel drug used in the treatment of cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction.[19] It belongs to the class of piperazine and has been approved for use in patients with chronic stable angina by the US Food and Drug Administration in 2006[20] and by the European Medicines Agency in 2008. This drug is characterized by a short biological half-life and this is a limit in maintaining the desired concentrations in the blood and determined the need for the development of a modified release drug delivery system.

Based on the possibility to use sIPN as a tool to obtain RNZ sustained-release dosage form, in this work, coated alginate and alginate-HPC pellets containing RNZ were formulated; the aim was to minimize the drug release in acidic environment and to control the drug release at the intestinal level in order to complete the drug release process in about 8 h. The goal of this study was to define the formulation and the coating composition of biopolymeric multi-unit systems for improving their technological and biopharmaceutical properties. In particular, Eudragit L100 (EU L100) and Eudragit L30 D-55 (EU L30)-coated alginate and alginate-HPC RNZ pellets were prepared by ionotropic gelation starting from a polymeric solution composed of SA (1.5%) or SA (1.5%) and HPC at 3 different concentrations (0.50%, 0.65%, and 1.00% wt/wt) and applying different percentages (5%, 10%, 20%, and 30% wt/wt) of coating material on pellet surface.

Materials and Methods

Materials

RNZ was kindly donated by Procos (Novara, Italy), SA (1% water solution viscosity 20 cps; ratio of mannuronic-guluronic residues = 1.56) was bought from Sigma-Aldrich (St. Louis, MO), and Klucel MF Pharm (HPC) (molecular weight = 850,000 g/mol, 2% water solution viscosity 4675 mPas, molar substitution 3.8, degree of substitution 74.1%) was purchased by Ashland (Milan, Italy). EU L100 and EU L30 were supplied by Evonik Industries (Gaggiano, Italy). All other materials were of analytical grade and used as received.

Methods

Formulation Development

SA (1.5% wt/wt) and HPC were dissolved in purified water under stirring. When the polymers were completely dissolved, RNZ (5.0% wt/wt) was added: a first rough dispersion was obtained and the formulation was sonicated (Branson 3510) for 30 min to ensure that no aggregates of drug particles were present and to form a homogenous suspension. In Table 1, the composition of the different formulations is reported.

The suspensions, kept under stirring (800 rpm), were added drop wise to a 100 mM calcium chloride gelling bath using a 600-μm diameter needle and a peristaltic pump (Masterflex C/L). The flow rate of the suspensions was regulated to obtain a constant stream of regular shaped drops.

The pellets were kept in the gelling bath under gentle stirring (300 rpm) for 15 min to assure the obtainment of desired mechanical properties. After 15 min, the pellets were recovered, washed with purified water to remove the excess of calcium ions from their surface, and dried in an oven at 40°C overnight.

Table 1
Composition of the Polymeric Formulations

Formulation	Concentration		
	HPC (% wt/wt)	Alginate (% wt/wt)	RNZ (% wt/wt)
RNZ 0	0.00	1.50	5.00
RNZ 0.5	0.50	1.50	5.00
RNZ 0.65	0.65	1.50	5.00
RNZ 0.75	0.75	1.50	5.00
RNZ 1	1.00	1.50	5.00

Coating of Alginate-Ranolazine Pellets

Two different polymers were utilized for the coating of alginate-RNZ pellets: EU L30 (poly(methacrylic acid-co-ethyl acrylate) 1:1-EU L30) and EU L100 (poly(methacrylic acid-co-methyl methacrylate) 1:1-EU L100). The pellets were coated using a fluidized bed bottom spray coater (STREA 1; Aeromatic-Fielder, Bubendorf, Switzerland; batch size: 500 g) equipped with a Wurster insert (a 70-hole bottom plate and a cylinder with 5 cm in diameter and 18 cm in height). Talc (50% on polymer weight) and triethyl citrate (10% on polymer weight) have been added to the EU L30 dispersion. Ten percent of EU L100 plus 1% triethyl citrate in a H_2O/EtOH solution (50/50) was applied. In Table 2, the conditions selected for the coating process are reported.

Morphological Characterization

The shape of uncoated pellets was observed using a stereomicroscope (Nikon SMZ-U) equipped with a camera (ZEISS Axiocam ICc 1) connected to an image analysis software. The image analysis software was also used to determine the mean diameter, the perimeter, and the area of pellets. The shape factor (*Sf*) was used to evaluate the roundness of the units and the formula used to calculate it is reported below:

$$Sf = \frac{4\pi A}{P^2}$$

where A is the area of the pellet surface while P is the perimeter. *Sf* can range from 0 to 1; when a sphere is analyzed the *Sf* is equal to 1.[21]

To gain more detailed information on the superficial and internal structure of pellets, samples were analyzed with a scanning electron microscope. The pellet morphology was examined by scanning electron microscopy (SEM; Hitachi S4700 field emission gun, Hitachi High-Technologies Europe, Krefeld, Germany) with a voltage of 5.0 kV; the magnifications are indicated within the corresponding figure. Upon observation the samples have been covered with a fine carbon layer in vacuum.

Drug Content

The drug content was determined by accurately weighing the pellets (10 mg) in 25 mL volumetric flasks. The flasks were then filled with sodium phosphate buffer pH 6.8 and stirred for 6 h to ensure the complete dissolution of the drug. The samples were

Table 2
Set of Conditions in the Coating Process

Coating Parameters	EU L30	EU L100
Ø nozzle (mm)	0.8	0.8
Air inlet temperature (°C)	38/42	36/40
Air outlet temperature (°C)	31/33	30/32
Internal temperature (°C)	36/38	34/36
Air flow rate (m^3/h)	120	115
Air pressure (bar)	1.2	1.2
Feed rate (g/min)	2	4
Air drying temperature (°C)	36/38	34/36
Drying time (min)	15	10
Curing	40°C/2 h	60°C/2 h