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Self-emulsifying excipient platform for improving technological properties of alginate–hydroxypropylcellulose pellets

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ABSTRACT

In this work, alginate, alginate–pectin and alginate–hydroxypropylcellulose pellets were produced by ionotropic gelation and characterized. Ibuprofen was selected as model drug; it was suspended in the polymeric solution in crystalline form or dissolved in a self-emulsifying phase and then dispersed into the polymeric solution. The self-emulsifying excipient platform composed of Labrasol (PEG-8 caprylic/capric glycerides) and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), able to solubilize the drug was used to improve the technological and biopharmaceutical properties of the alginate pellets. The pellets had diameters between 1317 and 2026 μm and a high drug content (>51%). DSC analysis showed the amorphous state of drug in the pellets containing the self-emulsifying phase. All the systems restricted drug release in conditions simulating the gastric environment and made the drug completely available at a pH value typical for the intestine. Only alginate-HPC systems containing the drug solubilized into the self-emulsifying phase showed the ability to partially control the release of ibuprofen at neutral pH. The self-emulsifying excipient platform is a useful tool to improve technological and biopharmaceutical properties of alginate–HPC pellets.

1. Introduction

Polysaccharide hydrogels show many advantageous properties such as non-toxicity, biodegradability and biocompatibility due to the resemblance of their structure with many body components. Their properties and compatibility with common pharmaceutical techniques explain the extensive use of polysaccharides as excipients in oral delivery systems (Beneke et al., 2009). Physically cross-linked polysaccharide gels are of great interest, particularly because the gel formation can be often carried out under mild conditions and in the absence of organic solvents (Coviello et al., 2007). Alginates are a series of unbranched polysaccharides, obtained usually from brown algae, and composed of guluronic (G) and mannuronic (M) acid residues that could be present as both homosequences and heterosequences (Lee and Mooney, 2012). Gelation of alginate is based on the affinity of this polymer towards divalent and trivalent ions as Ca^{2+}, Sr^{2+}, Ba^{2+} and Al^{3+} and on the ability to bind these ions selectively and cooperatively (Draget et al., 1997). The interactions of divalent ions with the G-blocks on the alginate chains induce the cross-linking of the polymer through a process called ionotropic gelation. The formed gel has a three-dimensional network structure, commonly described as "egg-box" structure. Ion-cross-linked alginate has usually low mechanical stability, a drawback which can produce fast drug release; a strategy to improve the mechanical stability of alginate gels in aqueous media is the blending of additional polymers in the alginate solution (Sosnik, 2014). Pectin is a family of complex polysaccharides present in the wall that surrounds growing and dividing plant cells. Pectin is primarily a polymer of D-galacturonic acid. The principal and key feature of all pectin molecules is a linear chain of α (1-4)-linked D-galacturonic acid units. The galacturonic acid polysaccharides are rich in neutral sugars such as rhamnose, arabinose, galactose, xylose and glucose (Beneke et al., 2009). Pectin is resistant to proteases and amylases of the upper

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gastrointestinal tract, while selectively digested by the microflora present in the colon; these characteristics make this polysaccharide particularly suitable for colon delivery of drugs (Wong et al., 2011). Pectin beads and microspheres cross-linked with calcium ions have been developed for the controlled release of various drugs, in particular for minimizing the release of the drug in the stomach and targeting it at the intestine level (Alvarez-Lorenzo et al., 2013). Alginate–pectin cross-linked pellets result in a more sustained release of diclofenac than pellets of pectin or alginate alone (Pillay and Fassihi, 1999) and in slow and controlled release of aspirin in the pH range 1.2–8.2 (Jaya et al., 2009); nonetheless the addition of pectin to an alginate matrix is not able to slow the release of caffeine (Belščak-Cvitanović et al., 2015).

The use of ether cellulose derivatives (as hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose) to form semi-IPN systems with alginate has been investigated with the aim of obtaining controlled release systems (Matricardi et al., 2013).

In this work starting from the comforting results obtained in a previous study with a different drug (Segale et al., 2015), a self-emulsifying excipient platform composed of Labrasol (PEG-8 caprylic/capric glycerides) and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), able to solubilize the drug was used to improve the technological and biopharmaceutical properties of the alginate pellets. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, classified as a BCS class II molecule (Potthast et al., 2005; Bolten et al., 2013) was selected as model drug. Ibuprofen loaded alginate pellets could be a delivery system capable of addressing some of the drawbacks of the drug, in particular they could help to overcome the short half-life of the drug and the topical damage to the gastric mucosa inflicted by ibuprofen. In this study, alginate, alginate–pectin and alginate–hydroxypropylcellulose pellets were developed and characterized with the aim of targeting and controlling the release of the drug. The drug included into the pellets was suspended in the polymeric network in crystalline form or dissolved in the self-emulsifying phase dispersed into the polymeric network.

2. Materials

Ibuprofen (IBU) was bought from ACEF (Fiorenzuola d'Arda, Italy), sodium alginate (SA) (molecular weight 120000–190000 g/mol; ratio of mannuronic-guluronic 1.56) and pectin (from citrus peel, galacturonic acid ≥74%, methoxy groups ≥6.7%) were bought from Sigma-Aldrich (St Louis, MO, USA), hydroxypropylcellulose (Klucel MF Pharm, molecular weight 850000 g/mol, viscosity 2% water solution 4000–6500 mPas) was provided by Ashland, Labrasol® (PEG-8 caprylic/capric glycerides, HLB value of 14) was kindly provided by Gattefossé (Milan, Italy), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) was a gift from Isochem (Gennevillers, France). All other materials were of analytical grade and used as received.

3. Methods

3.1. Formulation development

The polymeric phase was prepared by solubilizing under stirring the appropriate amount of alginate and HPC or pectin in water. Formulations constituted of crystalline drug (9.59%) suspended in the polymeric phase were prepared.

The solubility of ibuprofen in the self-emulsifying phase was determined to evaluate the right ratio between drug and excipients to use in the pellets. The solubility was determined by adding different, accurately weighed amounts of drug (from 20% to 60% w/w) to the excipient platform, by vigorously stirring the mixture for an appropriate time and by observing the samples at the stereomicroscope (Motic SMZ-168) to verify the dissolution of all drug crystals.

The self-emulsifying phase (SeP) was prepared by weighing Labrasol and TPGS in a beaker, respectively the 47.95% and the 4.10% of the total weight, then heating the mixture at 50 °C to melt TPGS and finally by adding ibuprofen, 47.95% of the total weight, to the excipients and stirring till the complete dissolution of the drug. The polymeric and the self-emulsifying phase were then mixed together in a 4:1 weight ratio till a homogenous and stable white emulsion was obtained.

In Table 1, the composition of the different formulations is reported.

3.2. Pellets production

Ibuprofen-loaded alginate pellets were produced through ionotropic gelation technique using an aqueous solution of calcium chloride 100 mM as gelling system. The biphasic mixture (suspension or emulsion) was added drop wise in the gelling bath through a G23 needle. The flow rate of mixture (4.2 mL/min) was regulated to obtain a constant stream of regular shaped drops. The pellets were left curing under stirring in the gelling bath for 15 min in order to allow the formation of the alginate network. After this time, the alginate pellets were recovered by filtration, washed with purified water to remove the excess of calcium ions and dried in an oven at 40 °C overnight.

3.3. Morphological characterization

Swollen and dried pellets were observed using a stereomicroscope (Motic SMZ168) to evaluate their morphology. Pictures of the pellets were taken using a Moticam 2500 camera linked to a PC. Diameter, perimeter and surface area of the pellets were calculated using the Motic Image Plus 2.0 software. The shape factor (Sf) was used to evaluate the roundness of the dried alginate pellets. The

Table 1
Composition of the formulations (polymeric and self-emulsifying phase were mixed in a 4:1 ratio).

Formulation	Polymeric phase			Self-emulsifying phase		Drug state
	Alginate (%)	HPC (%)	Pectin (%)	Labrasol (%)	TPGS (%)	
Alg	1.5	–	–	–	–	Cristalline drug
Alg SeP	1.5	–	–	47.95	4.1	Solubilized in SeP
HPC	1.5	0.75	–	–	–	Cristalline drug
HPC SeP 0.75	1.5	0.75	–	47.95	4.1	Solubilized in SeP
Pec	1.5	–	0.75	–	–	Cristalline drug
Pec SeP 0.75	1.5	–	0.75	47.95	4.1	Solubilized in SeP
HPC SeP 1.25	1.5	1.25	–	47.95	4.1	Solubilized in SeP
Pec SeP 1.5	1.5	–	1.5	47.95	4.1	Solubilized in SeP