European Journal of Pharmaceutics and Biopharmaceutics 87 (2014) 541–547

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Novel co-axial prilling technique for the development of core–shell particles as delayed drug delivery systems

Pasquale Del Gaudio, Giulia Auriemma *, Paola Russo, Teresa Mencherini, Pietro Campiglia, Mariateresa Stigliani, Rita Patrizia Aquino

Department of Pharmacy, University of Salerno, Fisciano, Italy

ARTICLE INFO

Article history:
Received 5 August 2013
Accepted in revised form 19 February 2014
Available online 26 February 2014

Keywords:
Co-axial prilling
Natural polysaccharides
Core–shell beads
Delayed drug delivery systems
Piroxicam
Chronotherapy

ABSTRACT

In this study, biocompatible double layered beads consisting of pectin core and alginate shell were prepared through a single step manufacturing process based on prilling apparatus equipped with co-axial nozzles. The core was loaded with piroxicam (PRX) as model non-steroidal anti-inflammatory drug (NSAID). Morphology, size distribution and shape of the double layered beads varied depending on the operative conditions and polymer concentrations. Co-axial nozzles size, applied vibration frequency, gelling conditions and, mainly, polymers mass ratio were identified as critical variables. Particularly, the relative viscosity of polymeric feed solutions inside the nozzle was the key parameter to obtain homogeneous and well-formed coated particles. The produced beads were investigated for the release kinetic in different media. Once PRX was encapsulated within the pectin core, a controlled release pattern was observed. Particularly, beads produced with 4:1 core/shell ratio (F4) released less than 30% of PRX in simulated gastric fluid (SGF) while total liberation of the drug was achieved during the next 3 h in simulated intestinal fluid (SIF). More interesting, F4 tested in SIF was able to release drug in a delayed and sustained manner at established time points (2h_8.2%, 3h_32.2%, 4h_70.1% and 5h_about 100%). Based on the above results, co-axial prilling approach is expected to provide success in manufacturing systems with delayed drug release profiles. Such systems may be potentially useful in targeting diseases which are affected by the circadian rhythm, such as chronic inflammation.

1. Introduction

In the last few years there has been a continuous research in the development of processes and techniques able to transform active pharmaceutical ingredients (APIs) into new dosage forms. The so-called "drug delivery systems" can modify biopharmaceutical and pharmacokinetic properties of the API, control its release rate, and obtain a site specific delivery, reducing side effects. All these aspects may increase the therapeutic efficacy and the safety of both new and old drugs allowing an optimal use in clinical practice [1,2].

In the field of oral controlled-release dosage forms, there has been a growing interest in chronotherapeutic drug delivery systems [3]. Some diseases like "early morning pathologies" show day-night patterns in the onset and symptoms exacerbation, usually with peaks in the morning and decrease throughout the day [4,5]. To enable the effective chronotherapy of such diseases, it is required a specific concentration of drug available at expected times [6–8]. This effect may be assured by dosage forms specially designed to release the API at predetermined rates, fitting with pathology requirements [4,9–15].

Among these pathologies, chronic inflammation and associated pain are related to plasma concentration of C-reactive protein (CRP) and interleukin-6 (IL-6), two systemic inflammatory mediators which follow a circadian cycle with predictable peaks in the morning [16,17]. Therefore, in this case the bed time administration of an anti-inflammatory delivery system with delayed drug release can provide an adequate symptoms control in the early morning, enabling an effective therapy [18–20].

Many technological approaches have been used to design controlled drug delivery systems tailored to follow the human chronobiological rhythm. In the last few years, several dosage forms such as osmosis-based monolithic formulations, swellable hydrogel devices, multi-unit tablets or floating dosage systems have been successfully developed [12,18,21–24].

Abbreviations: Alg, alginate; Pct, pectin; NSAID, non-steroid anti-inflammatory drug; PRX, piroxicam; SGF, simulated gastric fluid; SIF, simulated intestinal fluid.

* Corresponding author. Department of Pharmacy, University of Salerno, I-84084 Fisciano (SA), Italy. Tel.: +39 089969395; fax: +39 089969602.
E-mail address: gauriemma@unisa.it (G. Auriemma).

http://dx.doi.org/10.1016/j.ejpb.2014.02.010
0939-6411/

In this context, natural polysaccharides such as alginate and pectin continue to interest the scientific community due to their unique properties [25]. These polymers are particularly attractive because of their stability, non-toxicity and biodegradability. In addition, they are pH-sensitive and gel-forming. All these features coupled with the possibility to tailor their physico-chemical properties by chemical modification on the chain backbone structure make them ideal excipients to develop safe and efficient drug carriers for oral delivery [26–31].

However, oral formulations based on single polysaccharides usually exhibit an early release of the drug in the upper part of the GIT. Thus, they do not efficiently permit the delayed drug *in vivo* absorption required for the treatment of some diseases such as chronic inflammation. The appropriate combination of two or more polysaccharides may be an effective way to overcome this drawback [32–35].

In this paper we propose co-axial prilling technique as novel single step approach for the manufacturing of core–shell particles as delayed drug delivery systems. Prilling or laminar jet break-up has been considered a proper tool in creating polymeric hydrophilic microparticles (gel-beads) as modified delivery devices [36–39]. Moreover, the use of co-axial nozzles could be a strong improvement to obtain polysaccharide-based double layered beads consisting of amidated low methoxy pectin as core and alginate as shell. In this study piroxicam (PRX) was used as model non-steroidal anti-inflammatory drug (NSAID) loaded within the pectin core. Many process parameters were intensively investigated to find optimized conditions in order to produce uniform core–shell particle systems in a reproducible way. Particularly, polymers physico-chemical properties and concentration, solutions viscosity and feeds flow rate were studied as well as their influence in controlling PRX release rate.

2. Materials and methods

2.1. Materials

Amidated low methoxy pectin (LM pectin called GRINDSTED Pectin LA 415, DE 24% and DA 23%) was kindly donated by Dompè (Dompè s.p.a. l'Aquila, I).

Sodium alginate (European Pharmacopoeia X, MW ≈ 240 kDa) was purchased from Carlo Erba (Carlo Erba, Milan, I); zinc acetate dihydrate used as cross-linking agent was supplied from Sigma–Aldrich (Sigma–Aldrich, Milan, I). Piroxicam was kindly donated by Sifavitor (Sifavitor srl, Milan, I).

All other chemicals and reagents were obtained from Sigma Aldrich (Milan, I) and used as supplied.

2.2. Preparation and rheological studies of polymeric solutions

An appropriate amount of polymer (pectin or alginate) was dissolved in deionized water at room temperature under gentle stirring in order to obtain polymeric solutions with concentrations ranging between 1.5% and 8.0% w/w. Different amounts of solid crystalline PRX were suspended in the core polymer solution (pectin) and stirred for 2 h in order to obtain different drug/polymer ratios (1:20 and 1:10). The viscosity of each polymeric feed was measured by rotational rheometer (Bohlin Instruments Division, UK) where a cone-plate combination (CP 4/40) was used as measuring system.

2.3. Beads preparation

Drug loaded beads were manufactured by a vibrating nozzle device (Nisco Encapsulator Unit, Var D; Nisco Engineering Inc., Zurich, CH), equipped with a syringe pump (Model 200 Series, Kd Scientific Inc. Boston, MA, USA), pumping alginate solution and PRX/pectin suspension through a co-axial nozzle system (400 μm inner and 600 μm outer diameter, respectively). Other process parameters (volumetric flow rate = 10 ml/min, vibration frequency = 350 Hz, amplitude of vibration = 100%, droplets falling height = 25 cm) were established according to Cross model equation to obtain droplets coming out of the nozzle in narrow size distribution and avoiding satellite droplets formation [40]. Droplets were gelled under gentle stirring in an aqueous solution of zinc acetate (10% w/v) for 8 min at room temperature. Then, beads were recovered and thoroughly rinsed with deionized water. Finally, beads were dried at room temperature by exposure to air (22 °C; 67% RH) for several hours (12–18 h) until constant weight was reached. Moreover, blank beads were produced as control, processing alginate and pectin solutions in the above mentioned experimental conditions.

2.4. Beads size and morphology

Size distribution of hydrated particles was measured by an optical microscope (Citoval 2, Alessandrini, Milan, I) equipped with a camera whereas dried beads were analyzed by scanning electron microscopy (SEM), using a Carl Zeiss EVO MA 10 microscope with a secondary electron detector (Carl Zeiss SMT Ltd., Cambridge, UK), equipped with a LEICA EMSCD005 metallizator producing a deposition of a 200–400 Å thick gold layer. Analysis was conducted at 20 keV.

Projection diameter, of both hydrated and dried beads, was obtained by image analysis (Image J software, Wayne Rasband, National Institute of Health, Bethesda, MD, USA). A minimum of one hundred bead images were analyzed for each preparation in order to calculate length-number mean and relative standard deviation for at least three different prilling processes. Perimeter and projection surface area obtained by image analysis were used to calculate Sphericity Coefficient (SC) by the following equation [37,41]:

$$SC = \frac{4\pi A}{P^2} \quad (1)$$

where A is the projected bead surface area and P its perimeter.

Fluorescent microscopy images (FM) were obtained by analyzing cryofractured beads with a Zeiss Axiophot fluorescence microscope, with a 20 × 1.4 NA no-oil immersion plan Apochromat objective (Carl Zeiss Vision, München-Hallbergmoos, Germany) using standard DAPI (4′,6-diamidino-2-phenylindole) optics that adsorb violet radiation (max 372 nm) and emit a blue fluorescence (max 456 nm).

2.5. Calorimetric analysis

Raw materials, blank and drug loaded beads were analyzed by differential scanning calorimetry (DSC) on an indium calibrated Mettler Toledo DSC 822e (Mettler Toledo, OH, USA). Thermograms were recorded by placing accurately weighed quantities of each sample in a 40 μl aluminum pan which was sealed and pierced. The samples were heated from 25 to 350 °C at a scanning rate of 1 °C/min in nitrogen atmosphere at a flow rate of 150 ml/min. Melting temperature (T_m) and peaks intensity (mW) were measured for all samples and compared with each other. The analyses were carried out in triplicate.

2.6. Drug content and encapsulation efficiency

Beads PRX content was calculated as reported elsewhere [38]. Briefly, accurately weighed amounts of beads from each batch (about 30 mg) were dissolved under vigorous stirring in PBS buffer