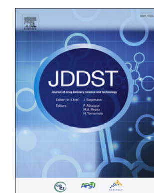
Journal of Drug Delivery Science and Technology 32 (2016) 126–131

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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



A novel core–shell chronotherapeutic system for the oral administration of ketoprofen

Andrea Cerciello, Giulia Auriemma, Pasquale Del Gaudio, Francesca Sansone, Rita P. Aquino, Paola Russo*

Department of Pharmacy, University of Salerno, I-84084 Fisciano, SA, Italy

A R T I C L E I N F O

Article history:
Received 30 April 2015
Received in revised form
2 July 2015
Accepted 24 July 2015
Available online 26 July 2015

Keywords:
Prilling
Zn-pectinate
Eudragit S100®
Core–shell particles

A B S T R A C T

The aim of a chronotherapeutic medicine is to tailor drug in vivo availability to circadian rhythms of diseases in order to reduce side effects and improve patient compliance. To counteract morning symptoms of early morning pathologies, a drug delivery system able to delay ketoprofen release after oral administration has been proposed. Particles made of a pectin matrix were produced by means of prilling; core–shell systems were produced covering the drug particles with Eudragit S100®. The systems developed, containing different drug/polymer ratios, were fully characterized in terms of drug content, efficiency of encapsulation, morphology and drug release kinetics. The results indicated that the loading of larger amounts of drug in the feed solution led to spherical and mono-disperse beads, with high encapsulation efficiency and a reduced drug delivery in gastric simulated fluids (22%). Finally, a further delay of drug release (7.3% released in simulated gastric fluid) was achieved applying to the drug/pectin core a shell of Eudragit S100® (40% w/w) a gastro-resistant polymer. This core–shell platform exploits the different characteristics of the two selected polymers, i.e. pH dependent solubility of Eudragit S100® and the peculiarities of pectin, degraded slowly in alkaline environment and selectively by the intestinal microflora in vivo.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

One of the most demanding technological challenges affecting the pharmaceutical industry is to adapt the release kinetics of the active ingredient to the therapeutic needs. Following this strategy, it is possible to increase the efficacy of the treatment and decrease side effects while improving patient compliance. This technological approach has favourable impacts, especially in the treatment of chronic diseases, such as inflammatory-based asthma, osteoarthritis and rheumatoid arthritis, also referred to as Early Morning Pathologies (EMP). The symptoms of the EMP worsen during the early morning hours, according to what can be called a circadian rhythm [1–3]. To counteract morning symptoms, a patient should take the medication during the night, or endure the pain waiting the action of the anti-inflammatory drug taken after waking up. A solution to these problems could be to design a pharmaceutical dosage form able to delay the release of the active ingredient, allowing the patient to take the medicine before going to sleep, enjoying its effects at early morning hours [4,5]. Moreover, Ollagnier and coll. reported that ketoprofen has a greater rate and/or extent of bioavailability when given in the morning than in the evening [6].

Usually, the materials used to control the release of a drug encapsulated are natural polymers such as sodium alginate, pectin, chitosan [7–10]. The choice of the polymer is crucial, because depending on its composition, structure and size, it is possible to transport the molecules and/or active materials through the different biologic substrates in order to obtain a therapeutic action targeted, site-specific and/or prolonged. An opportune tuning of drug release allows new therapeutic applications of active ingredients already known, as well as the technological transfer of the knowledge acquired on a drug model to other medicines "critics" with the ultimate goal of developing new and safer formulations. Often a single polymer cannot satisfy the need to release the medication in a specific district of the organism or in a precise moment of the day, thus making necessary the use of a polymeric blend or multiple layers of different polymeric materials [11–14].

Hence, in this research paper, particles (matrix systems) made of

* Corresponding author.
E-mail address: paorusso@unisa.it (P. Russo).

http://dx.doi.org/10.1016/j.jddst.2015.07.017
1773-2247/© 2015 Elsevier B.V. All rights reserved.

a pectin matrix and double layered particles (core–shell systems) made of a core of pectin and a shell of Eudragit S100® were formulated.

For the production of drug particles, pectin was selected as non-toxic, biocompatible and biodegradable polymer [15–17], ketoprofen, as anti-inflammatory drug model molecule [18,19]. The technique of prilling was selected among other methods of microencapsulation because it allows the production of spherical particles with a particle size distribution very narrow in mild operative conditions [20–22]. Pectin-Ketoprofen particles showing the best technological properties were selected as starting core material for the production of core–shell systems, covering the drug particles with Eudragit S100® an anionic copolymer of methacrylic acid and methyl methacrylate insoluble in acid pH.

2. Materials and methods

2.1. Materials

Amidated low methoxy pectin (esterification degree 24% and amidation degree 23%) was kindly donated by Herbstreith & Fox KG (Neuenburg, Germany); zinc acetate dehydrate used as cross-linking agent in aqueous solution ($Zn(CH_3COO)_2 \cdot 2H_2O$ granular) was supplied from Sigma–Aldrich (Milan, Italy). Ketoprofen was kindly donated by Dompè spa (L'Aquila, Italy); Eudragit S100® (Ph Eur) was purchased from Rofarma Italia srl (Milan, Italy). All other chemicals and reagents were obtained from Sigma Aldrich (Milan, I) and used as supplied.

2.2. Methods

2.2.1. Drug loaded beads

About 6 g of pectin precisely weighed were dissolved in deionized water at room temperature under gentle stirring in order to obtain 100 ml of polymer solution (6% w/w). Afterwards, different amounts of ketoprofen were suspended into the polymer solution and stirred for 2 h in order to obtain 3 different drug/polymer ratios in the pectin solution (1:20, 1:10 and 1:5 w/w). 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 the drug/polymer solution through a nozzle 400 μm in diameter. Experiments were performed at volumetric flow rate of 5 ml/min. Vibration frequency used to break up the laminar liquid jet was set at 350 Hz, amplitude of vibration 100%. The distance between the vibrating nozzle and the gelling bath was fixed at 25 cm. A stroboscopic lamp was set at the same amplitude as the frequency, in order to visualize the falling droplets. These latter were collected into an aqueous solution of $Zn(CH_3COO)_2 \cdot 2H_2O$ 10% (w/v) where they were gelified under gentle stirring. The beads were held into the gelling solution for 5–10 min at room temperature then recovered with a sieve and thoroughly rinsed with deionized water. Finally, the 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.

Acting on different operational parameters of the prilling equipment (frequency and amplitude of vibration, nozzle diameter, flow rate, etc.), it was possible to identify the optimal operative conditions in order to avoid the formation of satellite droplets in the process.

In particular, Zn^{2+} was selected as cross-linking agent since as reported elsewhere, zinc-pectinate beads were more appropriate compared with calcium-pectinate ones to resist in the upper gastro-intestinal tract and to refrain drug from premature release [23–25].

The optimized conditions allowed the production of hydrated homogeneous particles, with a spherical geometry and narrow size distribution. The hydrated gel-beads produced through prilling were then dried to increase product handling and stability.

Varying drug loading in the polymeric solution, 3 formulation were obtained: F20, F10 and F5, with a drug/polymer ratio of 1:20, 1:10 and 1:5. In addition, white beads of gel zinc pectinate (F) were produced as a control.

2.2.2. Core-shell systems

The enteric coating solution was prepared by dissolving Eudragit S100® in acetone at 6% (w/v) concentration; this solvent allowed complete dissolution of the enteric polymer while maintaining the integrity of beads. Coating was obtained by immersion of beads in the coating solution followed by solvent evaporation in a rotary evaporator. The process was repeated until the desired amount of coating was achieved. Microparticles were coated at different levels (weight increase ranging from 10% to 60%). Samples of coated beads were then dried and weighed; the mean coating weight was calculated by difference with respect to the initial beads weight.

2.3. Gel-beads characterization

2.3.1. Drug content and encapsulation efficiency

Dried bead samples of each manufactured batch (about 10 mg) were dispersed in 2 ml of phosphate buffer (100 mM, pH 7.0) and kept under vigorous stirring for 24 h, in order to disintegrate pectin matrix and to release the drug encapsulated. Afterwards, 23 ml of ethanol was added and the suspension was centrifuged at 6000 rpm for 15 min. Ketoprofen content was obtained by analyzing the solution spectrophotometrically at a λ of 254 nm (Evolution 201 UV/VIS Spectrometer, Thermo Scientific, Waltham; MA, USA). The actual drug content (ADC) was calculated according to:

$$ADC(\%) = \frac{drug\ content\ in\ dry\ beads}{weight\ of\ dry\ beads} \times 100 \quad (1)$$

Encapsulation efficiency was calculated as the ratio of actual to theoretical drug content. Each analysis was performed in triplicate, and the results were expressed as mean ± standard deviation.

2.3.2. Beads morphology

Size distribution and morphology of dried beads were determined by means of scanning electron microscopy (SEM) performed 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 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 a sphericity coefficient (SC) by the following equation:

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

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

2.3.3. Calorimetric analysis

Beads thermal characteristics were determined by differential scanning calorimetry (DSC) (Mettler Toledo DSC 822e module

Download English Version:

https://daneshyari.com/en/article/2483042

Download Persian Version:

https://daneshyari.com/article/2483042

Daneshyari.com