International Journal of Pharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Swellable floating tablet based on spray-dried casein nanoparticles: Near-infrared spectral characterization and floating matrix evaluation

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ARTICLE INFO

Article history:
Received 8 May 2015
Received in revised form 13 June 2015
Accepted 15 June 2015
Available online xxx

Keywords:
Casein nanoparticles
Genipin-crosslinking
NIR spectroscopy
Prolonged release
Spray-drying
Swellable floating tablet

ABSTRACT

In this study, spray-dried alfuzosin hydrochloride (ALF)-loaded casein (CAS) nanoparticles were successfully used for the preparation of a swellable floating matrix via direct compression. The developed NIR calibration model was able to assess ALF and CAS levels in five different batches of drug-loaded nanoparticles. The calibration and prediction plots exhibited good linearity with correlation coefficients of more than 0.9. The standard error of calibration and cross-validation was less than 5% of the measured values, confirming the accuracy of the model. A linear relationship was obtained correlating the actual drug entrapped and the predicted values obtained from the NIR partial least squares regression model. The un-crosslinked tablet demonstrated a substantial weight gain (317% after 2 h) and completely disintegrated after 3–4 h whereas both 10 and 40% w/w genipin-crosslinked tablets showed lower weight gain (114 and 42% after 2 h, respectively). A rapid floating of the tablets within 5–15 min (compared to 45 min for the marketed tablet) was observed, with maintained floating for 24 h. Marketed and prepared tablets succeeded to prolong ALF release for 24 h. The development of drug-loaded CAS nanoparticles using spray-drying represents a new alternative for the preparation of swellable floating tablets for prolonged drug release.

1. Introduction

Process analytical technology (PAT) is a system for designing, analyzing and controlling manufacturing processes based on an understanding of the scientific and engineering principles involved, and identification of the variables affecting product quality (Vredenbregt et al., 2003). Near-infrared spectroscopy (NIRS), Raman spectroscopy, Lasentec (focused beam reflectance measurement), biosensors and others are evolving PAT tools. NIRS is considered to be a quantitative, fast and nondestructive method used for routine identification and quality testing of incoming raw materials and content determination of active pharmaceutical ingredients (or API) in pharmaceutical preparations (Trafford et al., 1999). Several reviews have covered the application of NIR and NIR chemical imaging in pharmaceutical process monitoring as well as calibration and model development (Dou et al., 2007; Gendrin et al., 2008; Ravn et al., 2008; Zidan et al., 2010).

A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT) are poorly absorbed in the intestine, are unstable in lower parts of GIT, or are absorbed only in the initial part of the small intestine. Many sophisticated techniques have been utilized to develop floating devices, generally consisting of a capsule containing a drug reservoir and a floating reservoir filled with gas or containing a carbon dioxide generating blend. A simple method for producing floating systems uses polymeric materials with a density lower than that of the gastric fluid (Buri, 1985; Singh and Kim, 2000). The amphipathic nature of proteins, composed of polar and non-polar amino acid residues, causes them to concentrate at air–water or oil–water interfaces and to reduce surface or interfacial tension and therefore to reduce the mechanical energy required to form a foam or emulsion (Elzoghby et al., 2011). The emulsifying and foaming properties of sodium caseinate have been successfully utilized to prepare floating casein (CAS)–alginate and CAS–gelatin beads for controlled drug delivery (Bulgarelli et al., 2000; Mishra et al., 2008).

Alfuzosin (ALF) is a α_1-adrenoceptor blocker used clinically to alleviate the urine retention induced by benign prostatic hyperplasia. ALF HCl is characterized by high water solubility and rapid absorption together with a short half-life. The absolute bioavailability of ALF is about 49% under non-fasting conditions, while the

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http://dx.doi.org/10.1016/j.ijpharm.2015.06.015
0378-5173/

corresponding value under fasting conditions is around 25% (Liu and Fassihi, 2008). This shows that food has a significant impact on the oral absorption of ALF, potentially through the prolongation of gastric residence time. Moreover, ALF is preferentially absorbed in the proximal part of GIT and, in particular, the jejunum appears to be the main region for absorption (Maggi et al., 2000). As a result, prolonging the gastric residence time with a swellable controlled release gastro-retentive system allows continuous delivery of ALF from stomach to the intestine.

A 10 mg once-daily gastro-retentive extended-release ALF tablet is currently marketed under the brand name Uroxatral® which is more convenient for older patients. However, this formulation is a three layered Geomatrix™ tablet that is more costly and complex to produce that conventional formulation. In a study conducted by Liu and Fassihi (2008), gastro-retentive multi-layer tablet formulations of ALF HCl have been successfully developed based on polyethylene oxide, hydroxyl propyl cellulose (HPC) and hydroxyl propyl methyl cellulose (HPMC), and proved to be effective in providing prolonged flotation. In other studies, directly compressible tablet formulations of ALF were prepared using HPMC along with a directly compressible water insoluble polymer (Eudragit RS PO) which could prolong the release of ALF for 20 h (Nair et al., 2007; Roni et al., 2009).

Our group is engaged in the development of nanoparticulate drug delivery systems based on natural polymers including polysaccharides and proteins (Elgindy et al., 2011a; Elzoghby, 2013; Elzoghby et al., 2012a,b, 2015). Glutaraldehyde-crosslinked CAS microparticles have been studied for sustained delivery of water soluble drugs e.g. doxorubicin (Chen et al., 1987) and theophylline (Latha and Jayakrishnan, 1994). In recent years, CAS-based nanomicelles have been successfully used for solubilization and controlled release of various drugs e.g. mitoxantrone (Shapira et al., 2010), celecoxib (Bachar et al., 2012), cisplatin (Zhen et al., 2013) and flutamide (Elzoghby et al., 2013a,b,c,d).

In our previous study, spray-drying technique was successfully utilized for preparation of redispersible genipin-crosslinked CAS nanoparticles for prolonged release of ALF HCl. The results demonstrated a sustained drug release, with the % release monitored via modulating genipin-crosslinking density (Elzoghby et al., 2013e). In the present study, we demonstrated for the first time that spray-dried CAS nanoparticles could be utilized in the formulation of directly compressible floating ALF tablets without the need for any sophisticated techniques, based on their high swellability. The influence of genipin-crosslinking density on the properties of ALF tablets, including swelling, floating and release, was investigated. The aim of this research was extended to compare the floating and release performance of the prepared ALF tablets with the marketed tablet formulation.

2. Materials and methods

2.1. Materials

Alfuzosin hydrochloride (ALF) was kindly donated by Amriya Pharmaceutical Industries Co., PHARCO Corporation (Alexandria, Egypt). Bovine casein (CAS) was purchased from Sigma–Aldrich (St. Louis, USA). Genipin >98% was obtained from Synsci Pharmaceutical Co., Ltd. (China). All other chemicals were of analytical grade and used without further purification.

2.2. Preparation of ALF-loaded CAS nanoparticles

Solidified ALF-loaded CAS nanoparticles were prepared by using spray-drying technique as previously described (Elzoghby et al., 2013e). Briefly, the aqueous CAS solution (pH 7.4) containing ALF was spray-dried using a Büchi B-290 Mini-Spray Dryer (Flawil, Switzerland) at an inlet temperature of 150 °C, outlet temperature of 90 °C, feed flow of 5 mL/min, aspiration air of 90%, spraying pressure of 5.0–5.8 mbar and air flow rate of 320 L/h. Genipin was used to prepare crosslinked ALF-CAS nanoparticles by mixing ALF-CAS solution with genipin for 5 h before spray-drying.

2.3. NIR spectroscopy

For the five spray-dried nanoparticle formulations, NIR spectra were collected using a Büchi NIRFLEX N500 FT-NIR spectrometer (Büchi Labortechnik AG, Switzerland). The measurements were done in diffuse reflectance measurement mode using the solids measurement cell manufactured by the same supplier. Samples (200 mg) were measured directly through the base of the sample vials (16 × 46 mm size and 5 mL capacity).

It has been reported that glass vials are transparent to NIR beam and do not significantly affect the measured spectra (Cho et al., 2005). Each sample was measured three times and in between the measurement sequences, the vials were rotated by 120° in order to account for powder in homogeneities. Each collected spectrum was an average of 32 scans. Instrument resolution was set to 8 cm^{-1}. The acquisition wave number range was 4000–10000 cm^{-1}, and for the calculation of the PLS (partial least square) regression models, the range from 9000 to 10000 cm^{-1} was omitted due to the excessive spectral noise. In order to exclude any source of spectral variability due to variable quality of the borosilicate glass vials, and bulk density and particle size of the powder mixture, normalization pretreatments were applied in the modeling phase. Derivatives were applied as spectral pretreatments in order to enhance the spectral difference between the model substance and the protein carrier, i.e. to increase the specificity of the PLS regression model.

2.3.1. Exploratory analysis by principal component analysis method

Principal component analysis (PCA) was applied to the pretreated spectra of the calibration samples. The scores of the first and the second principal component of the PCA model were plotted together. The score clustering was observed and interpreted.

2.3.2. Development of the PLS regression models

For developing the NIR calibration models for the prediction of the model drug and the drug-carrier content, the partial least squares regression was used. It can be used to analyze data with strongly collinear, correlated, noisy and numerous *x* variables, and also simultaneously model several response variables (Bastien et al., 2005). PLS calibration models were developed using cross-validation approach (Xu and Liang, 2001). After the spectral acquisition step, the raw spectra were pretreated using the first derivative spectral pretreatment with the smoothing step (Blanco and Villarroya, 2002). Cross-validation procedure was done based on the target value. Seven cross-validation groups were formed including 5 different levels of the active pharmaceutical ingredient, pure polymer and pure drug. All replicates of the single sample were assigned to 1 respective group. The spectra of the same samples were placed in one cross-validation group. The number of principal components was chosen by observing the plot showing the dependence of the standard error of cross-validation against the number of principal components. The local minimum on the plot was the criterion to choose the adequate number of principal components, i.e., the complexity of the model.

2.3.3. Figures of merit of the PLS calibration models

The figures of merit were used to judge the quality of the developed calibration model. The standard error of calibration (SEC), standard error of cross-validation (SECV), coefficient of

Please cite this article in press as: Elzoghby, A.O., et al., Swellable floating tablet based on spray-dried casein nanoparticles: Near-infrared spectral characterization and floating matrix evaluation. Int J Pharmaceut (2015), http://dx.doi.org/10.1016/j.ijpharm.2015.06.015