Carbohydrate Polymers 98 (2013) 1317–1325

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

Physicochemical and molecular modeling studies of cefixime–L-arginine–cyclodextrin ternary inclusion compounds

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ARTICLE INFO

Article history:
Received 20 June 2013
Received in revised form 28 July 2013
Accepted 29 July 2013
Available online 3 August 2013

Keywords:
Cefixime
Cyclodextrin
L-arginine
Inclusion compounds
Spray drying
Ternary complex
Molecular modeling

ABSTRACT

In an attempt to improve the physicochemical properties of cefixime (CEF), its supramolecular inclusion compounds were prepared with β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HPβCD) in presence and/or absence of ternary component L-arginine (ARG) using spray drying technique. Initially, the phase solubility studies revealed a stoichiometry of 1:1 molar ratio with an A_L-type of phase solubility curve. The stability constants of binary systems were remarkably improved in presence of ARG, indicating positive effect of its addition. The inclusion complexes were characterized by FTIR, XRPD, DSC, SEM, particle size analysis, and dissolution studies. Further, molecular mechanic (MM) calculations were performed to investigate the possible orientations of CEF inside βCD cavity in presence and/or absence of ternary component. In case of physicochemical studies, the ternary systems performed well as a result of comprehensive effect of ternary complexation and particle size reduction achieved by a spray drying technology.

1. Introduction

An inclusion complexation with cyclodextrins is an interesting and extensively used one of the techniques for solubility/dissolution enhancement of poorly water-soluble drugs (Ficarra et al., 2000; Shah, Sancheti, Vyas, Karekar, & Pore, 2010). Cyclodextrins (CDs) are cyclic torus shaped oligosaccharides able to entrap a guest molecule spatially in their central hydrophobic cavity without any covalent interactions (Fernandes, Carvalho, Pereira da Costa, & Veiga, 2003; Stella & Rajewski, 1997). The outer surface of CDs is sufficiently hydrophilic to act them as potential solubilizing agents (Loftsson, Hreinsdottir, & Masson, 2005). The inclusion complexation of drug molecules with CDs usually results in favorable changes in the physicochemical properties of the drug, such as solubility, dissolution rate, stability and bioavailability (Aleem, Kuchekar, Pore, & Late, 2008; Doiphode, Gaikwad, Pore, Kuchekar, & Late, 2008) rendering them more suitable for oral drug delivery.

Although, CDs have been proved to be versatile carriers in pharmaceutical research, a large amount of CDs is frequently required to solubilize small amounts of a poorly water-soluble drug due to their lower complexation efficiency (Ribeiro, Loftsson, Ferreira, & Veiga, 2003). However, it is possible to improve the complexation efficiency of CDs by incorporation of small amounts of certain water-soluble auxiliary substances such as polymers (Gajare, Patil, Kalyane, & Pore, 2009; Valero, Perez-Revuelta, & Rodriruez, 2003), hydroxyl acids (Pokharkar, Khanna, Venkatpurwar, Dhar, & Mandpe, 2009) and/or amino acids (Bramhane, Saindane & Vavia 2011; Mura et al., 2005; Patil, Pore & Kuchekar 2008; Shah, Karekar, Sancheti, Vyas, & Pore, 2009) to the complexation media. Such systems, which are composed of three different molecular entities (drug, CD and an auxiliary substance) are often termed as supramolecular ternary complexes in which an auxiliary substance in conjunction with the CD, improves the desired physicochemical, and transport properties of a drug molecule. In addition to that, the third component enhances the efficiency of drug delivery with simultaneous reduction in the amount of CD required, thereby making the formulation of the final product cost-effective (Kurkov & Loftsson, 2012; Loftsson & Brewster, 2012).

Thus, considering all aspects of ternary systems, the efforts were undertaken to improve the physicochemical properties of a third generation broad spectrum oral cephalosporin (Markham & Brogden, 1995; Montay et al., 1991; Ziv, Lavy, Glickman & Winkler 1995) cefixime (CEF) (Fig. 1), via ternary complexation with CDs using an amino acid L-arginine (ARG) as an auxiliary substance. CEF chemically (6R,7R)-7[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino]-acet-amido)-8-oxo-3-vinyl-5-thia-1-azabicyclo-(4,2,0) octa-2-ene-2 carboxylic acid is a white to slightly yellowish crystalline powder, effective against wide variety of Gram-positive and Gram-negative aerobic bacteria. The presence

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http://dx.doi.org/10.1016/j.carbpol.2013.07.070

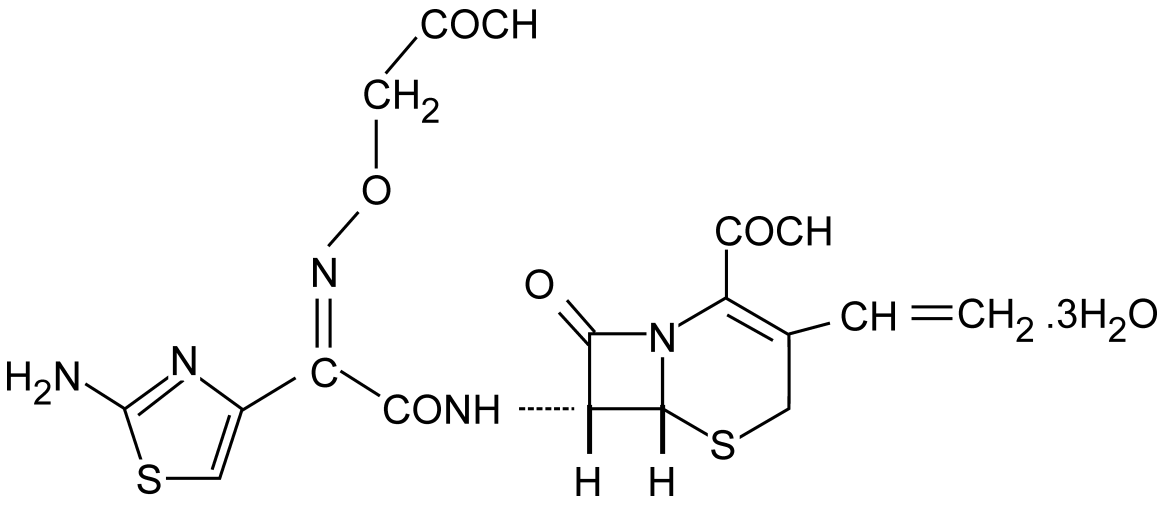

Fig. 1. Chemical structure of cefixime.

of 7-methoxyimine aminothiazole substituted cephem nucleus is a characteristic property of the third generation cephalosporins and confers excellent stability to CEF against β-*lactamases* type of enzymes (Genvresse & Carbon, 1993). However, poor aqueous solubility of CEF (Genvresse & Carbon, 1993; Markham & Brogden, 1995; Montay et al., 1991) contributes to its nearly 40–50% absorption (Genvresse & Carbon, 1993; Healy, Sahai, Sterling, & Racht, 1989) from gastrointestinal tract when administered orally. Poor aqueous solubility and hence the dissolution often result in variable bioavailability and limited therapeutic outcome of a drug.

The literature survey reported that few experiments on the effect of Captisol complexation on hydrolytic degradation of CEF in presence of polymers have been conducted where; stabilization of CEF has been shown to be achieved to some extent after Captisol complexation (Mallick, Mondal, & Sannigrahi, 2008). In this article, the authors report their investigations on preparation and characterization of inclusion compounds with cyclodextins for improvement of physicochemical properties of CEF. The spray drying technique was used to prepare inclusion complexes as particle size reduction to micron size by spray-drying technique is an adventitious approach as far as size and shape is concerned, also contributing to enhanced complexation efficiency thereby, performance of the inclusion complex (Kristmundsdottir, Gudmundsson & Ingvarsdottir 1996; Shah, Pore, Dhawale, Burade, & Kuchekar, 2012). The possible orientations of CEF inside a CD cavity in the presence and/or absence of ternary component were studied using molecular modeling and structural designing by computational chemistry methods. Further, molecular mechanic (MM) calculations were performed to optimize possible stoichiometry, geometry and stability of inclusion complex and as complementary evidences to support experimental studies. Initially phase solubility studies were conducted in distilled water to obtain the stoichiometry and the type of the solubility curve of the complex formation. The spray dried complexes were characterized by Fourier Transformation Infrared Spectroscopy (FTIR), X-ray Powder Diffractometry (XRPD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), particle size analysis and drug content uniformity studies. All systems including pure drug were further evaluated for their in vitro dissolution performance in 0.01 N HCl.

2. Material and methods

2.1. Materials

Cefixime was provided by Okasa Pharma, Satara, India, as a gift sample. βCD and HPβCD was kindly provided by Panacea Biotech, Chandigad, India. ARG and all other chemicals were purchased from Loba Chem, Mumbai, India, Analytical grade reagents and double distilled water were used throughout the experiment.

2.2. Phase solubility studies and interaction of CEF with CDs

The phase solubility studies in distilled water at room temperature (25 ± 2 °C) were performed in triplicate according to the method described by Higuchi and Connors (Higuchi & Connors, 1965). Excess amount of CEF (50 mg) was added to 20 mL of aqueous solution containing various concentrations of βCD or HPβCD (0–0.01 M) with or without addition of auxiliary substance ARG (0.25%, w/v). Then, the suspensions were mechanically shaken on rotary shaker for 96 hrs at 150 rpm. After equilibrium was achieved, the samples were filtered through 0.45 μm membrane filter and appropriately diluted. The concentration of CEF was determined spectrophotometrically (Shimadzu UV–vis spectrophotometer 1800, Japan) at 288.4 nm. The apparent stability constants (Kc) of the binary and ternary complexes were calculated according to the following equation:

$$K_c = \frac{\text{Slope}}{S_0(1 - \text{slope})} \quad (1)$$

where, S_0 is the solubility of CEF in absence of CDs.

The complexation efficiencies of CDs were also calculated from the following equation (Brewster & Loftsson, 2007).

$$\text{Complexation efficiency(CE)} = D_0 K_{1:1} = \frac{\text{Slope}}{(1 - \text{slope})} \quad (2)$$

where, D_0 is the intrinsic solubility of drug.

An indication of process of transfer of CEF from pure water to aqueous solution of HPβCD and βCD was obtained from the values of Gibbs free energy of transfer (ΔG_{tr}°) and it was calculated using the following equation:

$$\Delta G_{tr}^{\circ} = -2.303RT \log\left(\frac{S_c}{S_0}\right) \quad (3)$$

where, S_c/S_0 is the ratio of molar solubility of CEF in aqueous solution of HPβCD and βCD with or without auxiliary substance (0.25%, w/v) to that in distilled water in absence of HPβCD and βCD.

2.3. Molecular modeling studies

Molecular modeling was used to analyze the 3D geometry of CEF and βCD alone and in the complex by using VLifeMDS 4.1 software (VLife Sciences and Technologies, Pune, India). The MMFF program