Carbohydrate Polymers 152 (2016) 598–604

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

Stability of furosemide polymorphs and the effects of complex formation with β-cyclodextrin and maltodextrin

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ARTICLE INFO

Article history:
Received 9 March 2016
Received in revised form 28 June 2016
Accepted 2 July 2016
Available online 2 July 2016

Keywords:
Furosemide
Stability
Cyclodextrin
Maltodextrin
Solid state NMR
Polymorphism

ABSTRACT

The effect of the formation of supramolecular binary complexes with β-cyclodextrin and maltodextrin on the chemical and physical stability of the polymorphs I and II of furosemide was evaluated in solid state. The solid samples were placed under accelerated storage conditions and exposed to daylight into a stability chamber for a 6-month. Chemical stability was monitored by high performance liquid chromatography, while the physical stability was studied by solid state nuclear magnetic resonance, powder X-ray diffraction and scanning electron microscopy. Changes in the physical appearance of the samples were evaluated. The studies showed a significant stabilizing effect of β-cyclodextrin on furosemide form II. Our results suggest that the complex formation is a useful tool for improving the stability of furosemide polymorphs. These new complexes are promising candidates that can be used in the pharmaceutical industry for the preparation of alternative matrices that improve physicochemical properties

1. Introduction

Recently, much attention has been focused on the investigation of polymorphism of active pharmaceutical ingredients (API) due to its importance for the pharmaceutical technology industry. The presence of polymorphs often creates stability problems since they may have very different physical, chemical and mechanical properties such as melting points, solubility, dissolution rates, particle morphology, optical properties, chemical reactivity and physical stability (Bernstein, 2008; Braga, Grepioni, Maini, & Polito, 2009; Lee, Erdemir, & Myerson, 2011). The consequence is that, for example, at given conditions only one form is stable, and the other forms are metastable or definitely unstable. In addition, polymorphic changes from one form to another can strongly affect the bioavailability and therapeutic properties of an API, as well as the side effects of the product (Aaltonen et al., 2009). As these facts have a strong impact on the pharmaceutical development, the selection of the right solid state form is crucial for the production of reliable and effective pharmaceutical products.

The stability of APIs is in particular a matter of great concern because it affects the safety and efficacy of the drug product. The formation of degradation impurities may cause a loss of the efficacy of some APIs and initiate possible adverse effects. Therefore, the investigation of the chemical and physical stability of APIs is essential to ensure their quality and safety and applies a scientific and intelligent approach to formulation development.

Furosemide (FUR) is one of the most commonly used diuretic with rapid action that is normally administered as tablets or intravenous and intramuscular injectable products. It is a potent loop diuretic frequently used in the treatment of congestive heart failure, chronic renal failure, edemas, and hypertension (Prandota, 2002). FUR, which has seven polymorphic forms, contains a secondary amine group, and is therefore susceptible to acid catalyzed hydrolysis. At high temperatures, it hydrolyzes to 4-chloro-5-sulphamoylanthranillic acid and furfuryl alcohol which is quickly converted to levulinic acid. The photochemical degradation of FUR has been extensively reported. Several authors found that FUR exhibits photooxidation, photohydrolysis and photodechlorination (Bundgaard, Norgaard, & Nielsen, 1988; Chen & Burka, 2007; Kurmi, Kumar, Singh, & Singh, 2014; Vargas et al., 1998). According to the Biopharmaceutical Classification System (Custodio, Wu, & Benet, 2008), FUR is a class IV substance due to its low solubility and permeability. As a consequence, FUR has a poor oral bioavailability

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http://dx.doi.org/10.1016/j.carbpol.2016.07.006
0144-8617/

since it is preferentially absorbed in the gastric mucosa and upper intestine where it shows the lowest solubility.

In our recent studies, we reported useful strategies to enhance the drug bioavailability of FUR. In particular, new supramolecular complexes of forms I and II of FUR with maltodextrin (MD) and β-cyclodextrin (βCD) (Garnero, Chattah, & Longhi, 2013, 2014) improved the solubility and dissolution rate of the drug. We demonstrated that the binary complexes resulted in more effective drug delivery systems, providing an alternative to the preparation of matrices that enhance the oral bioavailability of FUR. However, no detailed evaluation of the stability of FUR polymorphs and the binary complexes in solid state is available.

In this work, we focused our study on polymorphs I and II of FUR in solid state. We evaluated the effect of the supramolecular binary complexes with βCD and MD on their chemical and physical stability, in particular, on the photochemical degradation processes of FUR. To investigate stability, the solid samples were placed under accelerated storage conditions and exposed to daylight into a stability chamber over a 6-month period. Chemical stability was monitored by high performance liquid chromatography (HPLC), while physical stability was studied by using solid state nuclear magnetic resonance (ssNMR), powder X-ray diffraction (PXRD) and scanning electron microscopy studies (SEM). In addition, the hygroscopicity was determined.

2. Experimental

2.1. Materials

Furosemide was provided by Parafarm (Argentina); β-cyclodextrin (MW = 1135) was kindly supplied by Ferromet agent of Roquette (France) and Maltodextrin (DE17) was given by Todo Droga (Argentina). All other chemicals used were of analytical grade and the solvents were of HPLC grade. A Millipore Milli Q Water Purification System (Millipore, Bedford, MA, USA) generated the water used in these studies.

2.2. Preparation of solid samples

2.2.1. Furosemide polymorphic forms

The two solid forms of FUR, I and II, were obtained as described in our previous reports (Garnero et al., 2013). Form I was recrystallized from a hot saturated solution of FUR in methanol, while Form II was obtained by evaporation under reduced pressure, from an acetone solution at 25 °C.

2.2.2. Binary systems

Solid-state binary systems of FUR polymorphs I and II in equimolar ratio with the ligands βCD and MD were prepared as previously reported (Garnero et al., 2013, 2014), and are summarized as follows:

2.2.2.1. Kneading method (KN). The systems FUR I:βCD (KN I_{CD}), FUR II:βCD (KN II_{CD}), FUR I:MD (KN I_{MD}) and FUR II:MD (KN II_{MD}) were prepared by accurately weighing appropriate amounts of the ligand and then transferring them to a mortar. An ethanol-water (50:50, v/v) mixture was added to the powder and the resultant slurry was kneaded for about 10 min. For each system, the corresponding solid form of FUR was added in small portions simultaneously with the solvent in order to maintain a suitable consistency. This slurry was kneaded thoroughly for about 30 min, and the resultant paste was dried in vacuum at 40 °C for 48 h, and protected from light.

2.2.2.2. Physical mixture (PM). Physical binary mixtures of FUR I:βCD (PM I_{CD}), FUR II:βCD (PM II_{CD}), FUR I:MD (PM I_{MD}) and FUR II:MD (PM II_{MD}) were prepared by simply blending uniformly the corresponding components with a mortar and pestle.

2.3. Content determination

For the determination of FUR content in the powders of each binary system, an amount of powder containing 10 mg of FUR was dissolved in a methanol-water (50:50, v/v) mixture. After appropriate dilution with mobile phase, the samples were analyzed with HPLC-UV, using a validated procedure described below. Each content determination was performed in triplicate and the average and standard deviations were calculated.

2.4. Stability design

To investigate the effect of complexation on the photodegradation processes of FUR polymorphs under accelerated storage conditions, the tests were executed following the requirements of the International Conference on Harmonization guidelines (ICH Q1A(R2), 2003). In order to perform the stability study, each FUR polymorph, the supramolecular complexes prepared using KN and their PMs were stored in triplicate in glass vials at 40 °C and 75% relative humidity (RH), and exposed to daylight into a stability chamber for 6 months.

2.4.1. Chemical stability study

To assess the chemical stability of the samples, the content of FUR was measured at established times of storage, initial time ($t = 0$), after three months ($t = 3$) and after six months ($t = 6$). The solid samples were dissolved and analyzed applying an HPLC stability-indicating method. The HPLC system was an Agilent 1100 (Agilent, Waldbronn, Germany). The HPLC experiments were performed under isocratic conditions. The samples were prepared in duplicate and the results were expressed as means of the three determinations in each one. *Chromatographic conditions*: the column used was a Phenomenex Gemini C18 250 mm × 4.6 mm i.d. filled with 5 μm particles, and with a precolumn (guard cartridge SecurityGuard C18 4 mm × 3.0 mm i.d.) supplied by Phenomenex (Torrance, CA, USA); the mobile phase was prepared with phosphate buffer(0.01 M KH_2PO_4 adjusted to pH 3.0)-acetonitrile 60:40 (v/v), filtered through a 0.45 μm Millipore membrane and degassed prior to use; the optimum flow rate was 1.5 mL min^{-1}; the column temperature was 25 °C, and the injection volume was 20 μL. The detection wavelength was set at 276 nm. The experimental conditions were set up to avoid interferences from the degradation products.

2.4.2. Physical stability study

In order to evaluate possible solid phase transformations, the physical stability of the samples FUR I, FUR II, KN I_{CD} and KN II_{CD} was analyzed by using the following techniques: Solid-state NMR spectroscopy (ssNMR), Powder X-ray Diffraction (PXRD) and Scanning electron microscopy (SEM) at the initial time ($t = 0$) after three months ($t = 3$) and after six months ($t = 6$) of storage.

High-resolution solid-state ^{13}C spectra of samples were recorded using the ramp cross polarization/magic angle spinning (CP-MAS) sequence with proton decoupling during acquisition (Harris, 1994). All ssNMR experiments were performed at room temperature in a Bruker Avance II spectrometer equipped with a 4 mm MAS probe, operating at 300.13 MHz for protons. The operating frequency for carbons was 75.46 MHz. Glycine was used as external reference for the ^{13}C spectra and to set up the Hartmann–Hahn matching condition in the cross-polarization experiments. All the spectra were recorded with 1600 scans, a contact time of 2 ms during CP and a recycling time of 5 s. The spinning rate for all the samples was 10 kHz. ^{1}H spin-lattice relaxation