International Journal of Pharmaceutics 511 (2016) 913–920

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

New multifunctional pharmaceutical excipient in tablet formulation based on citric acid-cyclodextrin polymer

Maria José Garcia-Fernandez[a,b], Nicolas Tabary[a], Feng Chai[b], Frédéric Cazaux[a], Nicolas Blanchemain[b], Marie-Pierre Flament[b], Bernard Martel, Pr.[a,*]

[a] Université Lille 1, Unité Matériaux et Transformations (UMET) UMR CNRS 8207, Villeneuve d'Ascq, France
[b] Univ. Lille, Inserm, CHU Lille, U1008 - Controlled Drug Delivery Systems and Biomaterials, F-59000 Lille, France

ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form 15 July 2016
Accepted 25 July 2016
Available online 26 July 2016

Chemical compounds studied in this article:
Cycloheptaamylose
Beta-cyclodextrin (PubChem CID: 101136808)
Citric acid monohydrate (PubChem CID: 22230)

Keywords:
β-Cyclodextrin polymer
Multifunctional excipient
Direct compression
Tablets
Acute toxicity

ABSTRACT

A β-cyclodextrin (β-CD) polymer obtained by crosslinking β-CD with citric acid in its water-insoluble (PCD-I) and soluble (PCD-S) forms was used as a multifunctional direct compression excipient for tablet designing. PCD-I powder was obtained after grinding the solid fraction through a 200 μm grid. PCD-S powder was recovered after lyophilization or spray drying of the PCD-S aqueous solutions, eventually followed by a wet granulation step. Both PCD-I and PCD-S powders were characterized, separately and mixed in variable ratios, based on dynamic water vapor sorption, SEM, particle size distribution, tapped density, compressibility, and flowability. PCD-I and spray dried and lyophilized/wet granulated PCD-S, as well as the mixture PCD-I/PCD-S = 90/10, presented optimal free flowing characteristics. Then, PCD-I or PCD-S powders - separately or mixed in variable ratios - were used for tablets preparation by direct compression without adding any other excipient (e.g. binder, lubricant, disintegrant etc). As PCD-I decreased, tablets resistance to crushing and disintegration time increased from 15 s to 15 min (against 30 min for β-CD), showing the improved disintegrant functionality of PCD-I, that rapidly swelled once in contact with water. Finally, PCD was force-fed to Sprague-Dawley rats (2 g/kg) which were then observed during 14 days for any clinical signs of toxicity.

1. Introduction

The European Medecines Agency (EMEA) defines pharmaceutical excipients as any constituent of a medicinal product that is not an active substance (EMEA, 2007). Based on this definition, adjuvants, stabilisers, antimicrobial preservatives, diluents, and antioxidants are all considered excipients. Within the drug dosage form technology field, there is an increasing interest on employing multifunctional excipients, with additional properties in drug forms other than their original function (tablet binder, lubricant, tablet disintegrant, coating agent, solubilizing agent, stabilizer in disperse systems, etc.) (Aleeva et al., 2009; Deepak and Gaurav, 2013). For example, the Ludipress® from BASF, a commercially available multifunctional excipient, is a unique three-in-one system combining the strengths of commonly used excipients: lactose as a carrier and filler, Kollidon 30 as a binding agent, and Kollidon CL as a disintegrant. Together, they form a granulate with excellent flowability, low hygroscopicity, plus outstanding binding power able to quickly and easily create homogeneous mixtures with the active ingredient, and to directly compress high-quality tablets.

Cyclodextrins (CDs), especially α-CD, β-CD, hydroxypropyl-β-CD, methyl-β-CD and sulfobutylether-β-CD, are pharmaceutical excipients present in injectable solutions, sprays, eye drops, powders and tablets with a good toxicological profile particularly in comparison to organic solvents, surfactants or water soluble polymers (Arima et al., 2011; Irie and Uekama, 1997; Stella and He, 2008). They are able to solubilize poorly soluble drugs via the formation of drug-cyclodextrin inclusion complexes (Loftsson and Brewster, 2012). However, β-CD often used in tablets compositions do not present optimum compression capabilities, as they are characterized by low fluidity which prevents free flow. In addition, β-CD displays the lowest solubility in water compared to other CDs derivates. As a consequence, β-CD based tablets preparation requires the

* Corresponding author at: Université Lille1, Unité Matériaux et Transformations, Bâtiment C6, Bureau 119, 59655 Villeneuve d'Ascq, France.
E-mail address: bernard.martel@univ-lille1.fr (B. Martel).

http://dx.doi.org/10.1016/j.ijpharm.2016.07.059
0378-5173/

addition of other excipients such as lubricants, disintegrants and binders. Another important impediment to the use of CDs is the weight of the pharmaceutical ingredient (API)-cyclodextrin complex containing the API dose (Loftsson and Brewster, 2012). In solid dosage forms, cyclodextrins can only be used in association with active pharmaceutical ingredients (API) with excellent affinity (i.e. a high complexation constant). If not, a significant amount of CDs needs to be incorporated into the formulation and the total amount of powder becomes too large for a single dose tablet. In this context, polymers of cyclodextrins represent a valuable alternative as they present enhanced affinity with the API compared to cyclodextrins alone (Loftsson and Brewster, 2011, 2012; Loftsson et al., 2005).

In 2005, Martel and al. reported the synthesis of cyclodextrin polymers, obtained by a reaction of polycondensation between CDs, citric acid (CTR) as a cross-linker, and sodium hypophosphite as a catalyst (Martel et al., 2005; Martel et al., 2002; Weltrowski et al., 2002). In that study, the obtained polymers (called polyCTR-βCD) could be primarily water-soluble (PCD-S) or water insoluble (PCD-I), depending on the preparation conditions in general, and more specifically on the extension of the polymerization reaction. Thus, PCD-S consisted of a hyperbranched polymer made of cyclodextrins moieties linked to each other by citrate groups (reported in Fig. S1) with a molecular mass inferior to 100 kDa, while PCD-I had exactly the same chemical structure, but with a higher crosslinking degree and molecular weight which are responsible for its insolubility in water. Though, PCD-I present high swellability as it absorbs up to 10 times its own weight in water, forming a gel (Martel et al., 2002). In particular, the ability of PCD-S polymers to solubilize APIs in water has been widely reported: ethoxzolamine (García-Fernández et al., 2013), doxycyclin (Bakkour et al., 2006), baclofen, bupivacain, chlorpheniramine, ketonazole, paliperidone, promethazine, propanolol, risperidone, verapamil (Danel et al., 2013). Besides, materials functionalized with PCD polymers were shown to improve interactions with hydrophobic active molecules, such as, chlorhexidine (Tabary et al., 2014), paclitaxel (Sobocinski et al., 2014), ropivacaine (Vermet et al., 2014) and *tert*-butylbenzoic acid TBBA (Martin et al., 2013). However, the use of the PCD-I itself as an insoluble material for pharmaceutical purposes as excipient for solid dosage forms has not been investigated yet.

The aim of the present study was to take advantage of both the PCD-S and PCD-I fractions in the preparation of tablets obtained by a direct compression process. Due to their complementary physico-chemical properties (i.e. PCD-S's high complexing ability towards drugs and PCD-I's high swelling capacity in water), both polymers present ideal characteristics to produce a multifunctional excipient for oral administration. Indeed oral administration is the widest used and accepted route for drug delivery to the adult population, especially in chronic therapies (Ponchel and Irache, 1998; Roger et al., 2010). In the present work, a β-cyclodextrin polymer (PCD) was synthesized, and separated into its PCD-I and PCD-S fractions. PCD-I was ground through a 200 μm mesh grid, and PCD-S was collected as powder after spray-drying or lyophilisation. The collected PCD-I and PCD-S powders, alone or mixed in different ratios, were characterized by dynamic vapor sorption, SEM, measurement of particle size distribution, density, compressibility and flowability. Then, PCD-I or PCD-S powders pre-conditioned by wet granulation were used, separated or mixed in variable ratios, for tablets preparation by direct compression without adding any other excipient (binder, lubricant, disintegrant, etc). Tablets resistance to crushing and disintegration time were measured and PCD toxicity was tested on Sprague-Dawley rats.

2. Materials and methods

2.1. Synthesis of cyclodextrin polymers

Polymers of β-CD (PCD) were synthesized in a semi-industrial scale reactor, according to a method adapted from the previously reported laboratory scale process (Martel et al., 2005; Martel et al., 2002). β-Cyclodextrin (β-CD) was provided by Roquette (Kleptose®, Lestrem, France). Citric acid monohydrate (CTR) and sodium dihydrogen hypophosphite ($NaH_2PO_2 \cdot H_2O$) were purchased from Aldrich Chemicals (Saint Quentin Fallavier, France)

Aqueous solutions (1000 mL) of sodium dihydrogen hypophosphite (30 g/L), citric acid (CTR) (100 g/L) and β-cyclodextrin (100 g/L) were prepared by stirring at room temperature. Water was totally removed using a Rotavapor (Büchi, Flawil, Switzerland) and the resulting dried mixture was then heated at 140 °C in an oil bath during 90 min under vacuum. The crust coating the round-bottom flask was then dispersed in water and filtered through a sintered glass funnel to isolate the insoluble fraction (PCD-I). After drying at 90 °C, the raw PCD-I collected was treated with a milling system equipped with a rotor and a 200 μm grid (Pulverisette 14, Fristsch, Idar-Oberstein, Germany). The filtrate containing PCD-S was then concentrated and purified by ultrafiltration (Pellicon, Millipore® membrane cut off 8 kDa). Finally, PCD-S was recovered as a white powder by lyophilization or spray drying. Lyophilization was performed under a vacuum of 0.06 mbar and ice-condenser cooled at − 53 °C (Christ®, Osterode, Germany). A 10% (w/v) PCD-S solution was used for spray drying (B-290 model, Büchi, Switzerland), equipped with a 0.7 mm two fluid nozzle. The PCD-S solution feed rate was 0.3L/h, the air flow rate of the spray drying air was 550 L/h and the flow rate of the drying air was 36 m^3/h. The inlet temperature was set to 115 °C.

PCD polymers structure corresponds to a crosslinked polymer network where each β-CD moiety was linked to neighboring β-CDs through citrate crosslinks (Fig. S1 in Supplementary material). The weight composition of PCD, determined by 1H NMR, was estimated at 53 wt.% in β-CD moieties and 47 wt.% in citrate cross-links. The Molecular mass (Mw) of PCD-S was 36 500 g/mol (PI = Mw/Mn = 2.7) measured by size exclusion chromatography (SEC) in water equipped with a light scattering detector.

2.2. Physico-chemical characterization of PCD powders

2.2.1. Hygroscopicity

The water sorption-desorption isotherms of β-CD, PCD-S and PCD-I were measured with a thermogravimetric analyzer (Q5000 SA, TA Instruments, Guyancourt, France), consisting of a microbalance in which the sample and reference pans were enclosed in a humidity and temperature controlled chamber. The temperature was controlled by Peltier elements. The relative humidity (RH) was controlled by mixing dry (RH = 0%) and water saturated (RH = 100%) N_2 gas flows (global flow set to 200 mL/min) in the chamber. The relative humidity (RH) was controlled by mixing appropriate proportions (regulated by mass-flow controllers) of dry and wet streams of N2.

Firstly, the sample was placed into the chamber and dried at 60 °C and 0% RH until its weight was stabilized to 0.01% for 180 min. In the second step, the chamber temperature was decreased to 25 °C. The humidity was then increased stepwise (with RH plateaus of 2 or 5%) until RH value reached 98%. For each RH plateau, the weight change of the sample was stabilized to 0.01% for a time period varying between 180 and 360 min. The water desortion isotherm was then registered by decreasing RH down to 0% with 2% or 5% RH increments.