International Journal of Pharmaceutics 492 (2015) 40–45

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Drug-in-cyclodextrin-in-liposomes: A novel drug delivery system for flurbiprofen

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ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form 24 June 2015
Accepted 3 July 2015
Available online 7 July 2015

Keywords:
Flurbiprofen
Cyclodextrins
Liposomes
In vitro
In vivo
Bioavailability

ABSTRACT

A novel delivery system based on drug-cyclodextrin (CD) complexation and liposomes has been developed to improve therapeutic effect. Three different means, i.e., co-evaporation (COE), co-ground (GR) and co-lyophilization (COL) and three different CDs (β-CD, HP-β-CD and SBE-β-CD) were contrasted to investigate the characteristics of the end products. FP/FP-CD loaded liposomes were obtained by thin layer evaporation technique. Size, zeta potential and encapsulation efficiency were investigated by light scattering analysis and minicolumn centrifugation. Differential scanning calorimetry (DSC) and transmission electron microscopy (TEM) showed the amorphous form of complexes and spherical morphology of FP-HP-β-CD COE loaded liposomes. The pH 7.4 phosphate buffer solution (PBS) was selected as the medium for the in vitro release. Wistar rats were put into use to study the pharmacokinetic behavior in vivo. FP-HP-β-CD COE loaded liposomes showed the better physicochemical characters that followed the average particle size, polydispersity index, zeta potential and mean encapsulation efficiency 158 ± 10 nm, 0.19 ± 0.1, -12.4 ± 0.1 mW and $56.1 \pm 0.5\%$, separately. The relative bioavailability of FP-HP-β-CD COE loaded liposomes was 420%, 201% and 402% compared with FP solution, FP-HP-β-CD and FP-liposomes, respectively. In conclusion, the novel delivery system improved the relative bioavailability of FP significantly and provided a perspective way for delivery of insoluble drugs.

1. Introduction

Flurbiprofen (FP) is a phenyl alkanoic acid derivative and a family of non-steroidal anti-inflammatory drug (Fig. 1a). It is widely used in the treatment of arthritis since its first appearance on the market in 1977 in Europe. The most frequently reported side effects upon oral administration are abdominal discomfort and other gastrointestinal site effects (Begum et al., 2012). With the scarcely solubility in water, low bioavailability in vivo and severe side effect in gastrointestinal tract when administered orally, the dosage form design and preparation of FP is always met with various difficulties (Yasmin Begum et al., 2011). Therefore, to overcome these drawbacks, there is a need indeed to design a novel delivery system. In recent years, there are more and more articles reporting the injectable preparations improving FP's relative bioavailability and reducing the relevant side effects, like FP liposomes (Yasmin Begum et al., 2011), FP-axetil (Yamashita Kazunori et al., 2006), FP-loaded microemulsion (Park and Kim, 1999) and so on.

Liposomes are spherical vesicles of diverse sizes consisting of a lipid bilayer and aqueous center compartment that have been widely applied as a safe and potential carrier for various administration routes (Maestrelli et al., 2006). Properties of not only the encapsulated drug but also the preparation method are the factors affecting the entrapment efficiency. The incorporation of poorly water soluble drugs in the lipid bilayer is always restricted in terms of the drug-to-lipid mass ratio (McCormack and Gregoriadis, 1994). When accommodating lipophilic compounds in the lipid phase, some drugs can interfere with bilayer formation and stability (McCormack and Gregoriadis, 1998). To circumvent the drawback mentioned above, entrapping hydrophilic drug or cyclodextrin complexes in the aqueous phase of liposomes has been studied. In recent years, the new drug delivery has been investigated by lots of researchers (Lapenda et al., 2013; Marianecci et al., 2013; Laza-Knoerr et al., 2010).

Cyclodextrins are naturally available water-soluble cyclic oligosaccharidesα-1,4-linked-glucopyranose composed of six or

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http://dx.doi.org/10.1016/j.ijpharm.2015.07.011
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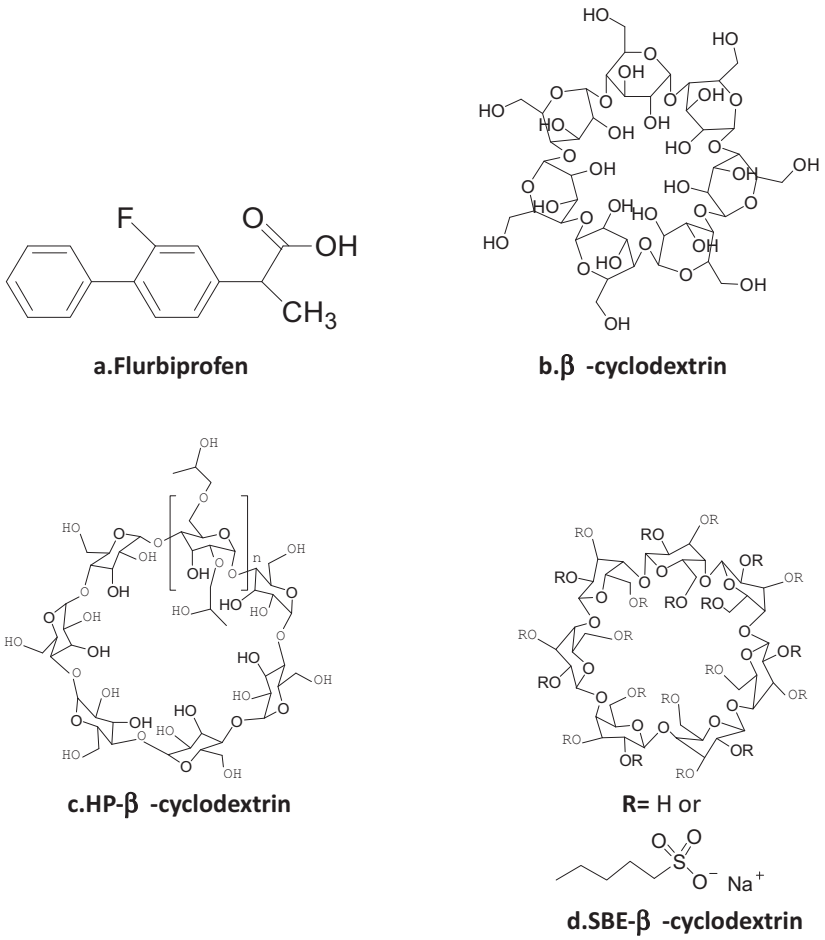

Fig. 1. Chemical structure of flurbiprofen (a), β-cyclodextrin (b), HP-β-cyclodextrin (c) and SBE-β-cyclodextrin (d).

more glucose units (Loftsson et al., 2005) (Fig. 1b). The unique structure and performance makes the inclusion inestimable, potential and actual value in various fields such as medicine, drug, agriculture, cosmetic, analytical chemistry and so on. Especially in the nearest few decades, the applications of cyclodextrins and their derivatives in the pharmacy have caught researchers' interest. Cyclodextrins are well known for their ability to increase solubility (Cirri et al., 2012), dissolution rate and bioavailability of the loaded drugs (Chen et al., 2007). In consideration of the problems associated with liposomes, the concept and attempt of entrapping water-insoluble drug in cyclodextrins then loaded in liposomes could potentially increase the drug to lipid mass ratio compared with the conventional drug incorporated into the lipid phase (Loukas et al., 1998). The improvement of dissolution and solubility for FP-β-cyclodextrin has been demonstrated (Muraoka et al., 2004). Derivatives like hydroxypropyl-β-cyclodextrin (HP-β-CD) (Fig. 1c) and sulfobutylether-β-cyclodextrin (SBE-β-CD) (Fig. 1d) with improved characters have been commonly used in recent years (Thompson, 1997). The two derivatives increased the solubility by more than 50% and had a more powerful solubilizing capacity than β-CD (Pitha and Pitha, 1985; Pitha et al., 1986; Müller and Branus, 1985). In addition, β-CD can be mixed in any proportion with a typical mixture of phospholipids and cholesterol to provide stable, spherical and unilamellar vesicles (Kauscher et al., 2013). The parenteral use of HP-β-CD has been studied and showed excellent safety profiles (Monbaliu et al., 1990; Frijlink et al., 1990). By combing the advantages of both liposomes and CDs together, the drawbacks of liposomes and the problems associated with CD complexes such as the toxicity to kidneys and rapid release when injected intravenously were ruled out (Vyas et al., 2008; Chen et al., 2014). Encapsulating of drug-cyclodextrin complexes into liposomes can increase the entrapment of the lipophilic drug and reduce its release from the carrier (Skalko et al., 1996). In addition, with a view to improving the solubility and delivery characteristics of poorly water-soluble drugs, formulation of β-cyclodextrin-curcumin (β-CD-C) inclusion complexes (hydrophilic curcumin) and entrapped both native curcumin (hydrophobic) and the complexes separately into liposomes were prepared (Rahman et al., 2012).

2. Matericals and methods

2.1. Materials

FP was purchased from Zhuhai Yuancheng pharmaceutical chemical Co., Ltd. (Guangdong, China). β-CD, HP-β-CD and SBE-β-CD were gifted by Xinda Fine Chemical Co., Ltd. (Shandong, China). Egg yolk lecithin and cholesterol (CH) were provided by Japan Co., Ltd. and Tianjin Bodi chemical Co., Ltd. (Tianjin, China), separately. Other chemicals and solvents were of analytical grade.

2.2. Preparation and characterization of FP-CD solid systems

Physical mixtures (PMs) of FP with β-CD, HP-β-CD and SBE-β-CD at the ratio of 1:2 (w/w) drug/carrier were prepared by blending the powder uniformly in a mortar. Co-ground (GR) products were obtained by kneading the CDs with just enough