European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 154–161

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of superdisintegrants

P. Srinarong *, J.H. Faber, M.R. Visser, W.L.J. Hinrichs, H.W. Frijlink

Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 23 February 2009
Accepted in revised form 15 May 2009
Available online 22 May 2009

Keywords:
Freeze drying
Solid dispersions
Fenofibrate
Superdisintegrants
Inulin
Polyethylene glycol (PEG)
Polyvinylpyrrolidone (PVP)
Mannitol
Hydroxypropyl-β-cyclodextrin

ABSTRACT

In this study, it was shown that the incorporation of superdisintegrants in solid dispersion tablets containing a high drug load can strongly enhance the dissolution rate of the highly lipophilic drug fenofibrate. In addition, the dissolution rate was more increased when the superdisintegrant was incorporated in the drug containing solid dispersions than when it was physically mixed with the solid dispersions. The dissolution rate enhancement strongly depended on the type of superdisintegrants and increased in the order Polyplasdone® XL-10 < Polyplasdone® XL ≪ Ac-Di-Sol® ≈ Primojel®. The dissolution behavior also depended on the type of hydrophilic carriers. Solid dispersion tablets based on inulin 4 kDa, polyethylene glycol 20 K and polyvinylpyrrolidone K30 showed a much faster dissolution than those based on mannitol and hydroxypropyl-β-cyclodextrin. Finally, inulin 4 kDa-based solid dispersion tablets showed excellent storage stability, while polyethylene glycol 20 K-and polyvinylpyrrolidone K30-based solid dispersion tablets did not.

1. Introduction

Solid dispersion technology can be applied to increase the dissolution rate of highly lipophilic drugs thereby improving their bioavailability [1–4]. Usually, solid dispersions are two-component systems consisting of a hydrophilic carrier in which the drug is incorporated. The drug incorporated in the hydrophilic carrier may be molecularly dispersed or may occur as nanocrystals or amorphous nanoparticles. The improved dissolution rate of the drug can be ascribed to (i) an increased solubility of the drug because of its amorphous state or small particle size (Kelvin's law) [5–8] (ii) an increasing surface area available for drug dissolution because of the small size of the drug particles [9,10] and (iii) an improved wetting of the drug caused by the hydrophilic carrier [11,12].

In a previous study, we investigated the dissolution behavior of solid dispersion tablets in which lipophilic drugs were incorporated in saccharide carriers. The dissolution of solid dispersion tablets was rapid when the carrier did not dissolve very slow or very fast and when a drug was incorporated in the carrier at a relatively low drug load. Obviously, when the carrier dissolves slowly, the drug will also dissolve slowly. However, the slow dissolution rate of the drug when using fast dissolving carriers and/or formulations with high drug loads was considered less obvious. We hypothesized that during dissolution of these tablets, the concentration of the drug in the near vicinity of the tablets became so high that uncontrolled crystallization of the drug occurred. Consequently, large drug crystals are formed which will dissolve slowly. This hypothesis was tested by analysis of remnants of the tablets which were taken out of the dissolution vessel after 2 h of dissolution. Indeed, these remnants consisted of pure drug which was fully crystalline [13]. Therefore, we investigated the effect of incorporating a surfactant, sodium lauryl sulphate (SLS), in solid dispersions on the dissolution behavior. It was expected that during dissolution, the high surfactant concentration in the near vicinity of the dissolving tablet would increase the drug solubility and thereby prevent crystallization of the drug. Indeed, it was found that the incorporation of SLS in solid dispersions strongly improved the dissolution rate of solid dispersions with a high drug load [14]. However, the amount of SLS incorporated in such solid dispersions had to be rather high which may lead to gastrointestinal tract irritation.

Another interesting method to improve the dissolution of solid dispersion tablets with a high drug load might be the incorporation of superdisintegrants in the solid dispersions because superdisintegrants do not irritate the gastrointestinal tract and can be used at low amounts in the formulations. We speculate that by the incorporation of superdisintegrants, the tablets will rapidly

* Corresponding author. Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. Tel.: +31 50 363 3254; fax: +31 50 363 2500.
E-mail address: P.srinarong@rug.nl (P. Srinarong).

0939-6411/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2009.05.006

disintegrate which prevents crystallization of the drug. Therefore, in the present study, we have investigated the effects of the following variables on dissolution behavior of solid dispersion tablets containing superdisintegrants: (i) the way to incorporate superdisintegrants in solid dispersion tablets, (ii) the type of superdisintegrants incorporated in solid dispersion tablets, and (iii) the type of hydrophilic carriers. In addition, the storage stability of some selected solid dispersion tablets was investigated. Fenofibrate was used as a model drug. Sodium starch glycolate (Primojel®), croscarmellose sodium (Ac-Di-Sol®) and two types of crosslinked PVP (Polyplasdone® XL and XL-10) were used as superdisintegrants. Inulin 4 kDa, polyvinylpyrrolidone (PVP) K30, polyethylene glycol 20 kDa (PEG 20 K), mannitol and hydroxypropyl-beta-cyclodextrin (HP-β-CD) were used as hydrophilic carriers.

2. Materials and methods

2.1. Materials

The following materials were used as supplied: fenofibrate and HP-β-CD from Sigma–Aldrich Chemie GmbH, Steinheim, Germany; inulin 4 kDa from Sensus, Roosendaal, the Netherlands; crosslinked PVP (Polyplasdone® XL and XL-10) from ISP, Wayne, USA; PVP K30 and SLS from BUFA B.V. Uitgeest, the Netherlands; PEG 20 K and tertiary butyl alcohol (TBA) from Fluka Chemie GmbH, Steinheim, Germany; mannitol (Pearlitol® SD) from Roquette, Lestrem, France; sodium starch glycolate (Primojel®) from DMV International, Veghel, the Netherlands; and croscarmellose sodium (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH-102) from FMC Biopolymer, Philadelphia, USA. Lipanthyl® tablets (145 mg fenofibrate tablets, Lot no. 12178, Expiry 12/2011) were purchased from Laboratoires Fournier S.A., Dijon Cedex, France. Demineralized water was used in all experiments.

2.2. Methods

Three different types of formulations were prepared: (1) solid dispersions composed of drug and carrier in which superdisintegrants were incorporated; (2) solid dispersions composed of drug and carrier physically mixed with superdisintegrants; and (3) physical mixtures of drug, carrier and superdisintegrant.

2.2.1. Superdisintegrants incorporated in solid dispersions

Solid dispersions were prepared by lyophilization as described before [15]. Briefly, fenofibrate was dissolved in pure TBA at a concentration of 12.5 mg/ml. Inulin 4 kDa, PVP K30, PEG 20 K, HP-β-CD or mannitol was dissolved in demineralized water at a concentration of 8.33 mg/ml. The superdisintegrants were dispersed in the aqueous solutions at a concentration of 0.696 mg/ml. Subsequently, these two solutions were mixed at a TBA/water ratio of 4/6 (v/v). The final concentrations of drug, carrier and superdisintegrant in the water/TBA mixture were 5, 5 and 0.42 mg/ml, respectively. Immediately after mixing, the solution was frozen in liquid nitrogen and then lyophilized. The formed solid dispersions all consisted of 48% w/w fenofibrate, 48% w/w carrier and 4% w/w superdisintegrant.

In a typical lyophilization cycle, the frozen solution was placed on the shelf of a Christ model Alpha 2–4 lyophilizer (Salm and Kipp, Breukelen, the Netherlands) with a condenser temperature of −53 °C. Lyophilization was performed according to a two-step procedure. First, the pressure was set at 0.220 mbar and the shelf temperature at −35 °C for one day. Subsequently, the pressure was decreased to 0.05 mbar, while the shelf temperature was gradually increased to 20 °C. This condition was maintained for another day. After removing the samples from lyophilizer, they were placed in a desiccator over siliga gel for at least one day before performing further experiments.

2.2.2. Superdisintegrants physically mixed with solid dispersions

For solid dispersions composed of drug and carrier physically mixed with superdisintegrants, only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. First, solid dispersions that consisted of 50% w/w fenofibrate and 50% w/w inulin 4 kDa were prepared by lyophilization as described above. Thereafter, Primojel® and solid dispersions were gently mixed by using a spatula and a mortar. The final powder mixture was composed of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. A solid dispersion without superdisintegrant at a drug load of 50% w/w was used as a control. The samples were stored at the same conditions as described in Section 2.2.1.

2.2.3. Preparation of fully physical mixture

For fully physical mixtures, only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. Fenofibrate, inulin 4 kDa and Primojel® were gently mixed by using a spatula and a mortar. The powder mixture consisted of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. The samples were stored at the same conditions as described in Section 2.2.1.

2.2.4. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC Q2000, TA Instruments, Ghent, Belgium) was used to determine the degree of drug crystallinity in solid dispersions. About 2–4 mg of sample in an open aluminium standard pan was heated at a scanning rate of 20 °C/min from a temperature −50 to 220 °C under a nitrogen gas flow. The heat of fusion of crystallized drug in solid dispersions was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was measured in a separate experiment. The ratio of the two fusion enthalpies was used to calculate the extent of relative drug crystallinity in solid dispersions. All experiments were conducted at least in duplicate. Calibrations of temperature and heat flow were carried out with indium.

2.2.5. X-ray powder diffraction (XRPD)

Samples were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, the Netherlands) with a copper anode (Cu Kα radiation, λ = 0.15405 nm, 40 kV, 40 mA). The diffraction pattern was measured with a step size of 0.008° and a dwell time of 45 s at each step between 4 and 50 2θ at ambient temperature.

2.2.6. Tableting

All powder combinations were compressed to flat and round tablets using an ESH compaction apparatus (Hydro Mooi, Appingedam, the Netherlands). Tablets containing 48 mg fenofibrate were prepared at a maximum force of 5 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 100 mg and 9 mm, respectively. Tablets containing the 145 mg drug were prepared at a maximum force of 10 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 302 mg or 640 mg and 13 mm, respectively. The 302 mg tablets were prepared from an inulin 4 kDa-based solid dispersion with Primojel® incorporated (145 mg fenofibrate, 145 mg inulin 4 kDa and 12 mg Primojel®). The 640 mg tablets were prepared from both the same amount and the same type of solid dispersions which was physically mixed with 338 mg Avicel® PH-102.

2.2.7. Disintegration test

The disintegration time of the tablets was determined in 900 ml of 0.5% w/v SLS at 37 °C using a USP disintegration test apparatus without disc (Erweka Apparatebau-GmbH, Heusenstamn Kr. Offenbach/Main, Germany). The samples were tested in triplicate.