Accelerated fenofibrate release from spray-dried microparticles based on polymer blends

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Fenofibrate-loaded microparticles based on PVP/Eudragit E or HPMC/Eudragit E blends were prepared by spray-drying. The composition of the systems (in particular the polymer/polymer blend ratio and the drug loading) was varied and the resulting key properties were determined (including drug release measurements in 0.1 M HCl, X-ray diffraction studies, solubility measurements and particle size analysis). For reasons of comparison, also the respective physical drug/polymer/polymer mixtures, microparticles based on binary drug/PVP and drug/HPMC blends, the fenofibrate powder as received and a commercially available drug product were investigated. Importantly, highly supersaturated fenofibrate solutions were created upon exposure of the different types of microparticles to the release medium, in contrast to any reference formulation. Also, the presence of co-dissolved Eudragit E led to a significant increase in fenofibrate solubility. At 10 % drug loading, all microparticles were amorphous and drug release stable during one month open storage. However, at 30 % loading, HPMC containing microparticles showed storage instability, due to drug re-crystallization.

Key words: Fenofibrate – Eudragit E – PVP – Spray-drying – Solubility enhancement – Supersaturation.

If a drug or drug candidate does not provide sufficient solubility in aqueous body fluids, it cannot reach its site of action in the living body and fails to show therapeutic efficacy *in vivo*, even if its chemical structure is ideal to interact with the target and *in vitro* studies show highly promising results. Formulators are more and more frequently confronted with this situation and a variety of strategies has been proposed to overcome the crucial hurdle of insufficient water-solubility. This includes the use of cyclodextrins [1], polymeric micelles [2], the transformation of crystalline drugs into an amorphous state [3-5], lipid formulations [6], co-crystals [7, 8], salt formation [7], particle size reduction [9, 10], and mesoporous systems [11]. A comprehensive overview of the different strategies used to prolong the life-time of supersaturated solutions has been published by Bevernage *et al*. [12]. Often, precipitation inhibitors are added [13]. If the formulation is administered orally, the presence of bile salts might also affect the absorption of poorly soluble drugs [14].

The general aims of the various approaches are to accelerate the process of drug dissolution, increase the apparent drug solubility, eventually create supersaturated solutions and keep them sufficiently stable to allow for increased drug absorption/transport away from the administration site and to provide long term stable drug delivery systems. The mathematical description of the physical processes involved in drug dissolution has recently been reviewed [15]. Different types of methods can be used to prepare such drug delivery systems with improved release of poorly water-soluble drugs, for example hot-melt extrusion [16, 17], film-freezing [18], and spray-drying [19] (amongst many other techniques). And different types of polymers have been reported to be useful to facilitate the dissolution/release of poorly soluble drugs, for example hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and poly[butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1/2/1 (Eudragit E). However, yet relatively little is known on the use of polymer blends and the impact of simply varying the polymer/polymer blend ratio on the key properties of the systems. From other fields, it is well known that polymer/polymer blends can be highly useful, since the systems' performance can effectively be adjusted by simply varying the blend ratio [20-23].

The aim of this study was to prepare different types of microparticles based on polymer blends by spray-drying. The impact of the type of blend, blend ratio and drug loading on the key features of the systems (especially drug release rates) were to be determined and better understood, based on X-ray studies, particle size and solubility measurements. Fenofibrate was chosen as poorly water-soluble drug. For reasons of comparison, also the drug powder as received, physical blends of the drug and the respective polymers as well as a commercially available drug product were investigated. Intentionally, non-sink conditions were provided in order to more realistically simulate *in vivo* conditions.

I. MATERIALS AND METHODS

1. Materials

Fenofibrate (Chemos, Regenstauf, Germany); hydroxypropyl methylcellulose (HPMC, Methocel E5; Colorcon, Dartford, United Kingdom); poly[butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1/2/1 (Eudragit E, Eudragit E 100 PO; Evonik, Essen, Germany); polyvinylpyrrolidone (PVP, Kollidon K30; BASF, Ludwigshafen, Germany); Lipanthyl 145 mg (Abbott, Abbott Park, Illinois, United States); acetonitrile (HPLC Grade; Fisher Scientific, Loughborough, United Kingdom); phosphoric acid 85 % (Sigma-Aldrich, Steinheim, Germany); ethanol 95 % (Brabant, Tressant, France).

2. Preparation of physical mixtures

Fenofibrate and one or more polymers (as indicated) were blended manually using a pestle and mortar for 10 min (100 g batch size). These blends were used for subsequent spray-drying or for *in vitro* drug release measurements.

3. Preparation of spray-dried microparticles

Drug-polymer blends were dissolved in 600 mL ethanol/water 85/15 (v/v). The liquids were spray-dried with a Buechi B-290 apparatus (Buechi, Basel, Switzerland), equipped with a 0.7 mm nozzle, using the following operating conditions: inlet temperature = 70 °C; aspirator flow rate = 36 m^3/h; drying gas flow rate = 414 L/h; feed

flow rate = 7.5 mL/min. The resulting outlet temperature was in the range of 40-45 °C.

4. *In vitro* drug release measurements

Fenofibrate release studies were performed using the USP35 paddle apparatus (Sotax, Basel, Switzerland) in 0.1 M HCl (500 mL; 37 °C; 75 rpm; n = 3) with appropriate amounts of formulations containing 145 mg fenofibrate. At predetermined time points, 3 mL samples were withdrawn (replaced with fresh medium), filtered through an Acrodisc (GxF/GHP 0.2μm, Pall, Port Washington, NY, United States), and subsequently diluted (1/1, v/v) with acetonitrile/water pH 2.5 (70/30, v/v) to prevent precipitation. The amount of fenofibrate in each sample was determined by HPLC analysis (ProStar 230 pump, 410 autosampler, 325 UV-Vis detector, and Galaxie software, Varian, Les Ulis, France). A reversed phase column C18 (Gemini 5 μm; 110 Å; 150 mm ×4.6 mm; Phenomenex, Le Pecq, France) was used. The mobile phase was acetonitrile/water pH 2.5 (70/30, v/v), the detection wavelength 288 nm and the flow rate 1 mL/min. One hundred µL samples were injected. The elution time was around 9 min. Each experiment (drug release and drug content measurements) was conducted in triplicate.

5. Determination of equilibrium solubility

The solubility at equilibrium of fenofibrate powder (as received) was determined in agitated flasks in 0.1 M HCl, optionally containing different amounts of PVP, HPMC and/or Eudragit E, as indicated. An excess amount of fenofibrate was exposed to 20 mL bulk fluid, kept at 37 °C under horizontal shaking (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Every 24 h, samples were withdrawn, filtered and analyzed by HPLC for their drug content (as described above) until equilibrium was reached. Each experiment was conducted in triplicate.

6. X-ray diffraction studies

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer equipped with a Cu X-ray tube ($\lambda_{CuK\alpha}$ = 1,540 Å) and the X'celerator detector. Powder samples were placed in a spinning flat sample holder, the measurements were performed in Bragg-Brentano θ-θ geometry.

7. Particle size measurements

Mean particle diameters were determined with an Axioscope microscope (Zeiss, Jena, Germany) and an optical imaging system (EasyMeasure; Inteq, Berlin, Germany). Each measurement included 200 particles.

II. RESULTS AND DISCUSSION

1. PVP/Eudragit E blends

The open circles in *Figure 1* show the dynamic changes in the concentrations of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The systems were based on different PVP/Eudragit E/drug blends, as indicated. Microparticles free of PVP could not be prepared, due to the low glass transition temperature of Eudragit E, resulting in intense sticking and film formation at the cyclone's wall [24]. For reasons of comparison, also the resulting dissolved drug concentration time profiles measured after exposure of: (i) the respective physical blends (open squares), (ii) fenofibrate powder (as received, filled squares), and (iii) the commercially available product Lipanthyl (filled diamonds), are illustrated in *Figure 1*. The dashed straight lines indicate the equilibrium solubility of fenofibrate powder (as received) in the presence of the respective amounts of Eudragit E and/or PVP (as incorporated in the microparticles). Importantly, the presence of co-dissolved Eudragit E led to increased fenofibrate solubility, whereas this was not the case for PVP (*Table I*). All spray-dried microparticles contained 10 % drug. In all cases, the amount of formulation exposed to the release medium contained 145 mg drug. All microparticle sizes were in the same order of magnitude (around 10 μm). This was also true for all other formulations in this study.

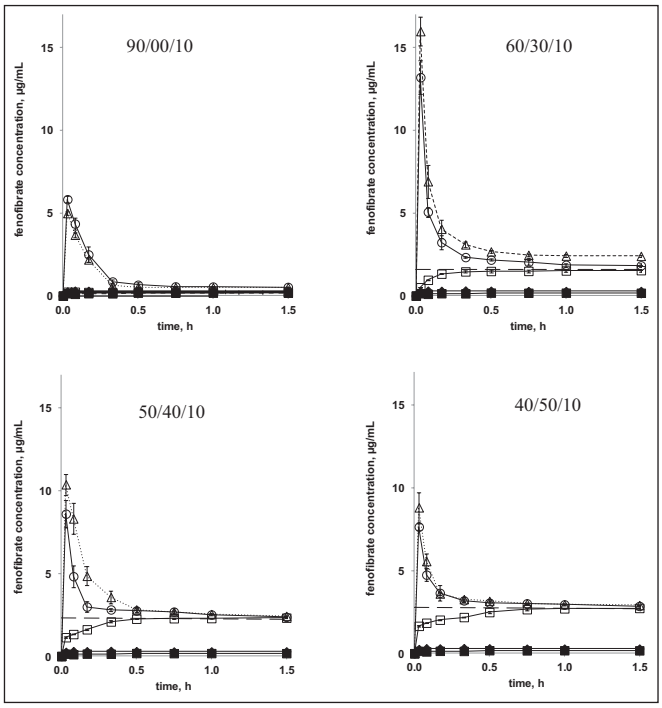

Figure 1 - Dynamic changes in the concentration of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The particles consisted of different PVP/Eudragit E/fenofibrate blends (the m/m/m ratios are indicated in the diagrams), all systems contained 10 % drug. The solid curves show drug concentration time profiles before storage, the dotted curves after 4 weeks storage at ambient conditions (in open vials). For reasons of comparison, also the resulting fenofibrate concentrations observed with the commercially available product Lipanthyl (filled diamonds), fenofibrate powder (as received, filled squares) and physical blends (open squares) are illustrated. The dashed straight lines indicate the equilibrium solubility of fenofibrate powder (as received) in the presence of the respective amounts of Eudragit E and PVP (as incorporated in the microparticles). In all cases, the amount of formulation exposed to the release medium contained 145 mg drug.

Table I - Equilibrium solubility of fenofibrate determined in 0.1 M HCl containing different amounts of PVP, Eudragit E and/or HPMC, at 37 °C.

Polymer(s)	Solubility (μg/mL, mean ± SD)
None	0.23 ± 0.03
0.26% w/v PVP	0.23 ± 0.03
0.17% w/v PVP + 0.09% w/v Eudragit E	1.58 ± 0.07
0.15% w/v PVP + 0.11% w/v Eudragit E	2.32 ± 0.03
0.11% w/v PVP + 0.15% w/v Eudragit E	2.78 ± 0.04
0.07% w/v PVP	0.23 ± 0.05
0.04% w/v PVP + 0.03% w/v Eudragit E	0.45 ± 0.13
0.26% w/v HPMC	0.52 ± 0.08
0.17% w/v HPMC + 0.09% w/v Eudragit E	2.27 ± 0.10
0.15% w/v HPMC + 0.11% w/v Eudragit E	2.81 ± 0.03
0.11% w/v HPMC + 0.15% w/v Eudragit E	3.41 ± 0.01
0.07% w/v HPMC	0.46 ± 0.05
0.04% w/v HPMC + 0.03% w/v Eudragit E	1.00 ± 0.07

Importantly, highly supersaturated fenofibrate solutions were almost instantaneously formed upon contact of all types of microparticles with the release medium. The highest concentration was achieved with 60/30/10 PVP/Eudragit E/fenofibrate blends. In all cases, the created solutions were metastable and the drug partially