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Preparation of polymeric fenofibrate formulations with accelerated drug release: Solvent evaporation versus co-grinding

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ABSTRACT

Polymeric fenofibrate-loaded films and particles aiming at improved dissolution of this poorly water-soluble drug were prepared by solvent evaporation or co-grinding. HPMC, PVP and PEG of various molecular weights were studied. In the case of HPMC, thin *films* were obtained when using the solvent evaporation method, whereas in all other cases *particles* were obtained. Interestingly, not only the type of polymer, but also the preparation method had a substantial impact on system performance and this in a not straightforward manner: For HPMC and PVP, solvent evaporation was much more efficient than co-grinding, whereas the opposite was observed with PEG. Fenofibrate was molecularly dispersed in HPMC and PVP, whereas it was partially dissolved and partially dispersed in the form of small crystals in PEG, irrespective of the type of preparation technique. Differences in the particle size could explain why drug release was faster from PVP-based systems prepared by solvent evaporation compared to co-grinding, and why the opposite was true in the case of PEG. For HPMC, differences in system homogeneity could explain the effects of the type of preparation method. Importantly, the drug dissolution rate and extent could be substantially increased, while assuring stability during at least 3 months open storage.

1. Introduction

As Rodriguez-Aller et al. [1] point out: "Poorly soluble compounds represent 40% of the top 200 oral drugs marketed in the US, 33% of drugs listed in the US Pharmacopeia, 75% of compounds under development and 90% of new chemical entities". This is why major research efforts are devoted to overcome this substantial bottle neck. If a drug cannot dissolve to a sufficient extent and at an adequate rate in aqueous body fluids, it is not able to reach its site of action. For instance, if the drug is administered orally, it first has to dissolve in the contents of the gastro intestinal tract (this means that the drug must be *molecularly* dispersed within the liquids) before it can be absorbed into the blood stream and distributed throughout the living organism. If the drug does not dissolve during its passage through the gastro intestinal tract, it is excreted with the feces. This is one of the most important reasons why novel and highly promising drug candidates (e.g. discovered during high-throughput screening campaigns in organic solvents) fail when they are first tested *in vivo*: Despite a potentially ideal chemical structure allowing to interact with the target site (when dissolved for instance in dimethyl sulfoxide *in vitro*), the treatment of a living organism is not effective, because the substance does not reach its target to a sufficient extent.

A variety of interesting strategies has been proposed to overcome this crucial hurdle by increasing the (apparent) *solubility* of the respective substance and/or its dissolution *rate*, using for example cyclodextrins (forming freely water-soluble complexes) [2], surfactants [3] and polymeric micelles [4] (incorporating the drug within hydrophobic micelle cores), lipid-based dosage forms [5,6] and liposomes [7] (dissolving the drug in hydrophobic phases), nanocrystals (due to the small particle size) [8,9], co-crystals [10,11], mesoporous systems [12] and amorphous systems (due to a higher energetic state of the drug compared to its pure crystalline form) [13–17] and/or dosage forms based on hydrophilic polymers, in which the drug is already molecularly dissolved (thus, avoiding the drug dissolution step). Special attention should be paid to the long term stability of these systems, particularly if the drug is in an energetically unfavorable physical state [18]. Different preparation

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methods can be used to obtained such advanced drug delivery systems for poorly water-soluble drugs, for example spray-drying [19,20], hot-melt extrusion [21–24], melting techniques [25], thin film freezing [26,27], (co-)grinding [28,29] and/or solvent evaporation techniques [30]. Also, theoretical methods can be very helpful to facilitate the development of novel drug products in this highly challenging field, for instance aiming at the prediction of drug solubility [31].

It has to be pointed out that upon oral administration the conditions *in vivo* in the gastro intestinal tract are decisive and can be complex, involving for instance pH-dependent drug solubility, super-saturation effects and drug re-precipitation [32]. To minimize re-precipitation phenomena, appropriate inhibitors might be added [33]. Furthermore, bile salts might play a crucial role *in vivo* [34]. Due to the complexity of the underlying mass transport mechanisms and large variety of possible drug–excipient combinations and manufacturing procedures, generally product optimization is based on cost-intensive and time-consuming series of trial-and-error experiments. Often, the effects of formulation and processing parameters on the resulting system performance are only observed, but not fully understood.

The aim of this study was to investigate the impact of the type of preparation technique (solvent evaporation versus co-grinding) and type of polymer used to prepare fenofibrate-loaded films and particles on the key properties of the systems. Particular emphasis was placed on a thorough physico-chemical characterization of the different formulations in order to better understand the observed drug release kinetics. Note that in this study, intentionally non-sink conditions were provided during the drug release experiments, in order to better simulate the conditions in the gastro intestinal tract [32].

2. Materials and methods

2.1. Materials

Fenofibrate (PCAS, Turku, Finland); poly(vinylpyrrolidone) (PVP 17, 25, 30; Kollidon 17 PF, 25, 30; BASF, Ludwigshafen, Germany); hydroxypropyl methylcellulose (HPMC E5, E15, E50; Methocel E5 premium LV, E15 premium LV, E50 premium; Colorcon, Kent, UK); poly(ethylene glycol) (PEG 1500, 3000, 4000, 6000; polyglykol 1500 S, 3000 S, 4000 S, 6000 S; Clariant, Burgkirchen, Germany); dichloromethane, methanol and acetonitrile (Fisher scientific, Illkirch, France); phosphoric acid (Sigma–Aldrich, Steinheim, Germany).

2.2. Preparation of polymeric fenofibrate particles and films

Different types of polymeric fenofibrate particles and films were prepared, either by a solvent evaporation method or by co-grinding, as described in the following.

Solvent evaporation method: Two grams of the pure drug or drug:polymer blends (10:90 w:w) were dissolved in 100 mL of a 95:5 (v/v) mixture of dichloromethane:methanol under magnetic stirring. The solutions were dried in a rotary evaporator at 40 °C (Rotavap R-215, Buechi, Flawil, Switzerland) and the obtained powders (in the case of pure fenofibrate and fenofibrate:PEG blends) or films (in the case of fenofibrate:PVP and fenofibrate:HPMC blends) were further dried at 40 °C for 24 h in a desiccator under vacuum. When removing the fenofibrate:PVP films from the glass walls of the rotary evaporator using a spatula, the films were mechanically too fragile to stay intact and broke into small fragments. Thus, also in this case, drug-loaded polymeric *particles* were obtained.

Co-grinding method: Three grams of the pure drug or drug:polymer blends (10:90 w:w) were milled under a dry nitrogen atmosphere for 12 h at 400 rpm in a high energy planetary mill (Pulvrisette 7, Fritsch, Idar-Oberstein, Germany). To minimize sample heating, milling was not continuous: Milling periods of 10 min were separated by 15 min periods without milling.

2.3. Drug release measurements

Ten milligrams of pure fenofibrate or an appropriate amount of fenofibrate formulation containing 10 mg of fenofibrate were exposed to 100 mL demineralized water (in flasks) at 37 °C under horizontal shaking at 80 rpm (GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time points, 3 mL samples were withdrawn, filtered [5 μm filter (BD, Franklin Lakes, USA), followed by a 0.2 μm PTFE filter (VWR, Fontenay-sous-Bois, France)], appropriately diluted and measured for their drug content by HPLC analysis, similar to [35] [Prostar 230, UV detector Prostar 325, Galaxie software (Varian, Middelburg, The Netherlands); octadecyl silane column (150 × 4.6 mm Gemini 5 μm

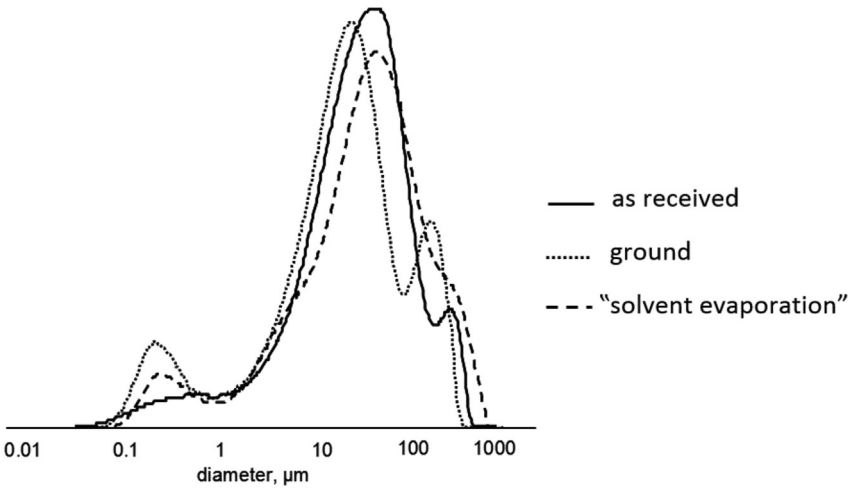

Fig. 1. Particle size distributions of the investigated fenofibrate powders: (i) as received, (ii) ground, or (iii) dissolved in dichloromethane:methanol and subsequently dried ("solvent evaporation").