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Research paper

Prilling of fatty acids as a continuous process for the development of controlled release multiparticulate dosage forms

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ABSTRACT

In this study, prilling was evaluated as a technique for the development of multiparticulate dosage forms using the fatty acids, stearic acid, and behenic acid as potential matrix formers to control the release of metoprolol tartrate (MPT), a highly water soluble drug. The in vitro drug release was dependent on the drug load, type of fatty acid, and pH of the dissolution medium. Higher drug loads resulted in faster release with behenic acid releasing drug over longer periods relative to stearic acid. The in vitro drug release was pH-dependent at low drug load with the release being slower at lower pH. Due to ionization of the fatty acid at pH 7.4, drug release was susceptible to the ionic strength at this pH value. Solid state characterization indicated that the crystalline state of the fatty acids was not affected by thermal processing via prilling, while the crystallinity of MPT was decreased. During storage, the amorphous MPT fraction recrystallized in the entire matrix. Drug release from behenic acid matrices was increased during storage at 40 °C; however, no polymorphism of behenic acid was detected. The bioavailability of MPT, after oral administration to dogs as prills containing 30% and 40% MPT using behenic acid as matrix former, was not significantly different from a commercial sustained release reference formulation, although the 40% MPT prills showed a burst release.

1. Introduction

The need for alternative excipients that allow for continuously producing solid dispersions to improve the dissolution of poorly water soluble drugs or to create sustained release dosage forms has been reported by different authors [1–4]. The application of oral sustained release formulations has improved patient compliance due to a lower dosing frequency and a reduced incidence of adverse side effects [5]. Moreover, the production of sustained release multiparticulate dosage forms is advantageous since their transport in the gastrointestinal tract is independent of gastric emptying and they exhibit a reduced risk of dose accumulation and local irritation when compared to single-unit dosage forms [6].

Lipid-based excipients such as triglycerides and fatty acids have been used for the development of solid dosage forms as matrices for controlled drug release [7–10], as taste-masking agents [11], to enhance drug solubility [12–14] and for the manufacturing of floating dosage forms [15,16]. Compared to polymers [17], triglycerides exhibit several advantages, including low cost, non-toxicity, and biodegradability. Nevertheless, their physical instability during storage (reflected in changes in the melting enthalpy and melting range which modify drug release [10]) remains the main barrier to overcome when applying these excipients for drug formulation [7,18].

While lipid-based solid dosage forms have been processed using techniques such as solid lipid extrusion [19], extrusion/spheronization [20], melt granulation [21], melt pelletization [7,9] and spray-congealing [13], prilling has received limited attention in the pharmaceutical industry as a technique to efficiently incorporate drugs in a multiparticulate lipid-based solid dosage form. The prilling process consists of pumping a mixture of drug and lipid through calibrated nozzles, creating a liquid jet. By applying vibrational energy, the liquid jet breaks up into droplets which are then cooled by falling through a temperature-controlled prilling tower [22]. This technique offers the advantage of obtaining in a continuous fashion spherically shaped particles with a narrow particle size distribution. Having excellent flow properties, the particles can be easily filled into gelatin capsules [23], creating a multiparticulate formulation. Additionally, no solvent is involved, resulting in a shorter and environmentally friendly pharmaceutical process. However, the major disadvantage of the prilling process is

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the need of a high prilling tower, linked to higher costs and difficulties in operation and maintenance [24].

The aim of this study was to evaluate the use of prilling for the manufacturing of multiparticulate dosage forms using fatty acids as potential matrix formers to control the release of highly water soluble drugs. For this purpose, stearic acid and behenic acid, C18, and C22 fatty acids, respectively, were combined with metoprolol tartrate (MPT) as model drug and the in vitro performance was assessed. The solid state of the formulations, termed "prills" further on in this study, was characterized using modulated differential scanning calorimetry (MDSC), X-ray diffraction (XRD), Raman spectroscopy, Raman microscopic mapping, and attenuated total reflection Fourier-transform (ATR FT-IR) spectroscopy. Furthermore, the physical stability of the prills during 6 months storage at 25 and 40 °C was monitored. Finally, the bioavailability of the different formulations was evaluated after oral administration to dogs and compared to a commercial sustained release formulation.

2. Materials and methods

2.1. Materials

Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) was selected as a model drug. Behenic acid (Radiacid 0560) was purchased from Oleon (Ertvelde, Belgium) and had a C22 purity of 89%. Stearic acid, with a C18 purity of 98.7%, was purchased from Mosselman (Ghlin, Belgium). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Prilling

Prilling was carried out with a custom-made prilling equipment developed by Peira (Turnhout, Belgium). After melting the fatty acid and heating the melt to 90 °C (stearic acid) or 100 °C (behenic acid), MPT was added to the melt under stirring. Droplet formation was started after complete dissolution of the drug in the molten matrix. By applying air pressure, the mixture was fed toward the thermostated nozzle (90 °C) equipped with a valve and a needle (inner diameter: 0.33 mm). To manufacture solid particles containing 10% MPT and using behenic acid as matrix former, a drop time (i.e., period during which the valve is open) of 0.04 s and an air pressure of 0.5 bar were applied, whereas the drop time and air pressure were set at 0.07 s and 0.5 bar for the 20% MPT and 30% MPT formulation. When the drug load was increased to 40%, a drop time of 0.07 s and a pressure of 1 bar were used. A drop time of 0.04 s and an air pressure of 0.5 bar were needed for all MPT/stearic acid combinations. Droplets formed at the needle end were quench cooled in liquid nitrogen in order to obtain solid spherical particles.

2.2.2. Particle size and shape

The particle size and shape were determined using an image analysis system. Photomicrographs of the prills were taken with a digital camera (Camedia® C-3030 Zoom, Olympus, Tokyo, Japan), linked with a stereomicroscope system (SZX9 DF PL 1.5x, Olympus, Tokyo, Japan). A cold light source (Highlight 2100, Olympus, Germany) and a ring light guide (LG-R66, Olympus, Germany) were used to obtain top illumination of the prills against a dark surface. The images were analyzed by an image analysis software (Analysis®, Soft Imaging System, Münster, Germany). At least 20 particles were analyzed from each batch. Each individual particle was characterized by the mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°). An average value for all prills has been calculated as the mean particle size (mean FD). To evaluate sphericity, particles were characterized by the aspect ratio (AR) (ratio of the longest Feret diameter and its longest perpendicular diameter).

2.2.3. In vitro drug release

In vitro dissolution was performed using USP dissolution apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system coupled with a VK 8000 automatic sampling station (Vankel, New Jersey, USA). An amount of prills corresponding to 30 mg MPT was inserted into the baskets. The basket rotational speed was set at 100 rpm and the temperature of the dissolution medium was maintained at 37 ± 0.5 °C. Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and analyzed spectrophotometrically at 222 nm using a double beam spectrophotometer (UV-1650PC, Shimadzu, Antwerp, Belgium). MPT concentrations were calculated from a calibration curve between 0 and 33 μg/ml. Demineralized water, 0.1 N HCl (pH 1), and a phosphate buffer (USP, pH 7.4) were used as dissolution media. The influence of the ionic strength μ on MPT release was studied in diluted phosphate buffer with $\mu = 0.0089$ (10-fold dilution), $\mu = 0.018$ (5-fold dilution) and $\mu = 0.045$ (2-fold dilution), phosphate buffer ($\mu = 0.089$), phosphate buffer with increasing NaCl concentrations ($\mu = 0.14$ and $\mu = 0.20$), 0.1 N HCl, and 0.1 N HCl with $\mu = 0.20$. Each experiment was performed in triplicate. The similarity between dissolution profiles was evaluated using the similarity factor f_2, according to Shah et al. (1998), and was calculated using the following equation (Eq. (1)):

$$f_2 = 50\log_{10}\left(\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} * 100\right) \quad (1)$$

where R_t and T_r represent the cumulative drug release at each sample point of the reference and the test sample with n equal to the number of sample points. As f_2 is sensitive to the number of sample points leading to bias, only one sample point exceeding a drug release of 85% was considered in the calculation. f_2 values higher than 50 indicate similarity between two dissolution profiles based on an average difference of less than 10%, while f_2 values below 50 represent significant differences [25].

2.2.4. Modulated differential scanning calorimetry

The thermal behavior of the pure compounds (MPT, stearic acid, and behenic acid), the physical mixtures, and the corresponding formulations was evaluated using a differential scanning calorimeter Q2000 (TA Instruments, Zellik, Belgium) equipped with a refrigerated cooling system. The DSC was calibrated for temperature and enthalpy using an indium standard. Tzero calibration was performed in two steps; baseline calibration (without samples or pans) and sapphire calibration (using large sapphire disks on both the sample and reference positions). Small sapphire disks, placed in a Tzero pan, were used for the heat capacity (MDSC) calibration. Samples (±5 mg) were run in Tzero pans (TA Instruments, Zellik, Belgium) with an underlying heating rate of 2 °C/min. The modulation period and amplitude were set at 60 s and 0.318 °C, respectively (heat-iso method). Dry nitrogen was used as a purge gas through the DSC cell at a flow rate of 50 ml/min. MDSC data were analyzed using the Universal Analysis software (TA Instruments). Melting enthalpies were determined in the total heat flow signal. Melting temperatures were reported as onset temperatures.

2.2.5. X-ray diffraction

Crystallinity was analyzed using X-ray diffraction on the pure compounds, the physical mixtures, and the corresponding formulations. X-ray diffraction was performed with a D5000 Cu Kα diffractor ($\lambda = 1.54$ Å) (Siemens, Karlsruhe, Germany) with a voltage