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# Melt extrusion process for adjusting drug release of poorly water soluble drug felodipine using different polymer matrices

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ABSTRACT

The purpose of the present study was to use commercial available polymers like PVP/PEG, soluplus® and kollidon® SR to prepare immediate and sustained release formulations of felodipine by hot melt mixing method. Solid dispersions containing 5, 10, 20 and 30 wt% drug have been prepared in a Haake-Buchler Reomixer at melt temperature 130 °C and mixing time 10 min. As was found from DSC and XDR studies completely amorphous and miscible solid dispersions can be prepared. In all cases a single glass transition was recorded, which is depended from the used drug amount. Hydrogen bonds and the molecular interaction between felodipine and polymer matrices are responsible for the miscibility of prepared formulations. This has as result the substantial enhancement of felodipine release rate in PVP/PEG mixture and due to the high solubility of used polymers immediate release formulations have been prepared. On the contrary, sustained release formulations can be prepared in the case of kollidon SR solid dispersions. The release mechanism of all preparations was studied using different kinetic models. Finally, binding affinity values calculated by molecular docking simulations were used as estimators for predicting long-term drug's physical stability in solid dispersions.

## 1. Introduction

Hot Melt Extrusion (HME), a simple and fast process for the preparation of drug solid dispersions, is applied in the pharmaceutical sector for more than 30 years (Kuentz et al., 2016; Repka et al., 2017; Repka et al., 2012; Patil et al., 2016). Based on this technique, pharmaceutical solid dispersions are prepared via co-melting and screw mixing of suitable polymers with proper active pharmaceutical ingredients (APIs). During preparation, the API is either dispersed or dissolved within a selected matrix-carrier, forming suitable pharmaceutical extrudates (Pawar et al., 2016). Both polymeric and inorganic (Maniruzzaman et al., 2015) based matrix-carriers can be used for the preparation of such systems. The resultant extrudates can be downstreamed by several ways, such as milling, spheronizing, granulating, compressing into tablets, filling into capsules etc., and administered into patients as per current regulatory guidelines (Maniruzzaman et al., 2012).

Today, HME has received considerable attention from both pharmaceutical industry and academia in a range of applications (including tablets, capsules, films, implants etc.), targeting several routes of administration, such as oral, transdermal, and trans-mucosal routes (Crowley et al., 2007). Furthermore, HME is widely applied for the preparation of pharmaceutical solid dispersions used to increase the solubility and hence, oral bio-availability of poorly water soluble APIs. Till today, except HME-based solid dispersions numerous approaches have been employed in order to increase API's aqueous solubility including particle size reduction, salt formation, prodrug formation, use of surfactants, cyclodextrin complexation, lipid based drug delivery systems, etc. (Bikiaris, 2011a, 2011b), each of which has its own advantages and limitations. Regarding the preparation of pharmaceutical solid dispersions, HME has many benefits compared to the other techniques such as solvent evaporation, spray drying, freeze drying, supercritical fluid processing, roll spinning etc. Specifically, it is a solvent free easy to scale up method, which is environmentally friendly and can be used as a continuous manufacturing process for the preparation of repeatable products with good content uniformity (Shah et al., 2013; Vithani et al., 2013). Hence, HME represents a novel continues mixing process which can be applied to melt or solubilize drug inside suitable

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matrices for the preparation of amorphous drug delivery systems that effectively enhance solubility and improve oral bioavailability of poorly water soluble APIs (Thiry et al., 2017).

After extensive researching, HME is now accepted as a robust method to produce almost all known drug delivery systems, like immediate, modified, controlled and drug targeted formulations (Vithani et al., 2013; Hasa et al., 2015; Loreti et al., 2014; Zhang et al., 2017; Vervaeck et al., 2015; Stanković et al., 2013; Bikiaris et al., 2009). However, and besides these extensive research attempts, HME has not yet been tested for the preparation of drug solid dispersions exhibiting different dissolution profiles for the same API (i.e. immediate and controlled/sustained release profiles). Hence, the aim of the present work is to use for the first time HME in order to prepare immediate and sustained release formulations of the poorly water soluble API felodipine, by using different polymer matrix-carriers appropriate for melt-extrution. In addition, it is the first time that molecular docking simulations are evaluated as a tool for the prediction of long-term physical stability of APIs in solid dispersions.

## 2. Experimental

### 2.1. Materials

Felodipine (Felo) with purity of 99.9%, melting point at 143–145 °C and solubility in water approximately 0.5 mg/L (while is freely soluble in ethanol) was obtained from PCAS (Longjumeau, France). Poly(vinyl pyrrolidone) (PVP) type Kollidon K30 with a molecular weight of 50,000–55,000, $T_g$ = 157 °C (DSC), moisture content 1.95% (TG) and bulk density 0.410 g/cm$^3$ was obtained from BASF Co (Ludwigshafen, Germany). Poly(ethylene glycol) with molecular weight 400 g/mol (PEG400) and moisture content 0.5% was supplied by Clariant (Germany). Soluplus® [poly(vinyl caprolactam)-poly(vinyl acetate)-poly(ethylene glycol) graft copolymer in a ratio of 13/57/30] with $T_g$ = 70 °C and molecular weight 118,000 g/mol. Kollidon® SR with k-value 60–65 and $T_g$ = 35 °C were obtained from BASF Co (Ludwigshafen, Germany). Kollidon® SR is a poly(vinyl acetate) (PVAc) and povidone (PVP) mixture consisted from 80% PVAc, 19% PVP, 0.8% sodium lauryl sulfate (SLS) and 0.2% silica. All the other materials and reagents were of analytical grade and purity.

### 2.2. Preparation of solid dispersions by hot melt mixing

Pre-weighed (a total of 10 g) solid dispersions of PVP/PEG 80/20 w/w and Felo at ratios 95/5, 90/10, 80/20 and 70/30 w/w were prepared by melt mixing in a Haake-Buchler Reomixer (Model 600) with roller blades. Before melt mixing, PVP and felodipine were dried by heating them in a vacuum oven at 80 °C for 24 h. The components (PVP/PEG and Felo) were physically premixed before being fed in the reomixer, to achieve a better dispersion of FELO in PVP/PEG mixture. Melt blending was performed at 130 °C for 10 min and 30 rpm roller speed. During the mixing period, the melt temperature was continuously recorded. Using the same Reomixer and the above mentioned conditions, soluplus/Felo and kollidonSR/Felo solid dispersions were also prepared with drug rations 95/5, 90/10, 80/20 and 70/30 w/w. All solid dispersions after preparation were ground in a freezer mill (Horiba Scientific 6770) and placed in desiccators at room temperature (25 °C) to prevent any moisture absorption.

### 2.3. Characterization of solid dispersions

#### 2.3.1. Differential scanning calorimetry (DSC)

Thermal behavior of solid dispersions was studied using a Perkin-Elmer Pyris Diamond differential scanning calorimeter. The instrument was calibrated with high purity indium and zinc standards. Samples of 6.0 ± 0.2 mg were used for the measurements. A constant nitrogen flow was maintained to provide a constant thermal blanket within the DSC cell, thus eliminating thermal gradients and ensuring the validity of the applied calibration standard from sample to sample. For each sample a cyclic scanning procedure was followed to record the thermal behavior of the material. Each sample was placed in aluminum seal and heated from 30 °C till 180 °C at a heating rate of 20 °C/min. The sample remained at that temperature for 2 min in order to erase any thermal history and remove the moisture traces. Following the samples were quenched at 30 °C with cooling rates 300 °C, remained at that temperature for 3 min and scanned again up to 180 °C using the same heating rate (20 °C/min).

#### 2.3.2. Wide angle X-ray diffractometry (WAXD)

WAXD was used for the identification of the crystal properties (structure and changes) of the pure materials and dispersion systems. X-ray diffraction measurements of the samples were performed using an automated powder diffractometer Rigaku Mini Flex II with Bragg-Brentano geometry (θ-2θ), using $CuK_\alpha$ radiation (λ = 0.154 nm) in the angle 2θ range from 5 to 55°.

#### 2.3.3. Fourier transformation-infrared spectroscopy (FT-IR)

FTIR spectra were obtained using a Perkin-Elmer FTIR spectrometer, model Spectrum 1000. In order to collect the spectra, a small amount of each material was used (1 wt%) and compressed in KBr tablets. The IR spectra, in absorbance mode, were obtained in the spectral region of 450 to 4000 cm$^{-1}$ using a resolution of 2 cm$^{-1}$ and 64 co-added scans.

#### 2.3.4. Scanning electron microscopy (SEM)

The morphology of the prepared solid dispersions was examined by a scanning electron microscopy system (SEM) JEOL JMS-840A equipped with an energy dispersive X-ray (EDX) Oxford ISIS 300 micro-analytical system. The samples were covered with carbon coating in order to increase conductivity of the electron beam. Operating conditions were accelerating voltage 20 kV, probe current 45 nA and counting time 60 s.

### 2.4. Dissolution experiments

In vitro drug release studies were performed as follows. Dissolution Apparatus I basket method was used on a Distek 2100C dissolution tester (Distek, North Brunswick, NJ). Weighed amounts according to containing 2.5 mg of FELO solid dispersions (monolithic formations) with particle sizes 150–200 μm (collected after sieving the milled particles) were filled in hard gelatin capsules manually, and placed into the baskets. Dissolution medium was consisted of 500 ml phosphate buffer and 2% Tween 20 (pH = 6.5), the stirring rate was kept constant at 100 rpm and the temperature also at 37 °C (Karavas et al., 2006). At predetermined time intervals (namely, 0, 5, 10, 15, 30, 45, 60, 90 and 120 min for immediate release and 0, 1, 2, 4, 6, 8, 10, 12, 16, and 24 h for controlled/sustained release formulations) 3 ml of aqueous solution was withdrawn from the release media. The withdrawn amount was substituted with the buffer solution used as release media. The samples were filtered and analyzed with the aid of a UV spectrometer at 362 nm.

### 2.5. Molecular docking simulations

Molecular docking simulations were performed in order to model the interactions between felodipine and melt-mixing polymers at the atomic level. All simulations were performed with the aid of AutoDock Vina software program using gradient local optimization algorithm and automate grid map generation (Trott and Olson, 2010). The starting coordinates of felodipine were taken from the crystal structure (CCDC Number 1144175). All polymer structures were prepared with the aid of XenoView v.3.7.9.0 (Shenogin and Ozisik, 2007). Molecular structures of pure PVP and PVA were used for simplicity (more complex structure will be computationally intensive) for modelling PVP-PEG and