Polyvinyl Alcohol in Hot Melt Extrusion to Improve the Solubility of Drugs

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Introduction
More than 80 % of current pipeline drugs and approximately 40 % of marketed drugs suffer from limited solubility, which can result in low or variable bioavailability of the active pharmaceutical ingredients (APIs) [1]. Hot melt extrusion (HME) is a solid dispersion technology whereby the API is dispersed, often down to the molecular level, into a polymer matrix through application of heat and mechanical energy and processes to form an amorphous solid solution [2]. The aim of this study was to evaluate a pharmaceutical-grade polyvinyl alcohol (PVA) as the matrix polymer for HME application. Therefore, performance characteristics such as API solubility enhancement, high thermal stability, and the stability of amorphous solid dispersions at high dose were analyzed.

Methods
Poorly water-soluble APIs classified as biopharmaceutics classification system (BCS) II class with different thermophysical properties were selected (Tables 2 and 3). Polyvinyl alcohol (Partec® MXP, MilliporeSigma) with an 87 – 89 % hydroylization grade, MW approx. 32,000 Da was selected as the thermoplastic polymer. Sorbitol (Partec® SI 150) and meglumine, both from MilliporeSigma, were selected as plasticizers. At first, a mixture of PVA and API (Table 2), or, if required, a mixture of PVA, API and plasticizer (Table 3) were completely blended using a Turbula® mixer (Bachofen AG, Muttenz, Switzerland). The mixture was then loaded into a twin screw extruder (Brabender® Mini-Compounder KETSE 12/36 D, Duisburg, Germany) with specific extrusion parameters; the setup of those parameters depended on the physical properties of the API. The obtained extrudate was cryo-micronized into fine particles (D<sub>50</sub> = 100 – 120 µm) and then analyzed using DSC (crystallinity) and HPLC (content); real-time dissolution analysis was done with a Sotax AT 7 system (Sotax AG, Basel, Switzerland).

Using PVA as a matrix polymer in HME, it is able to achieve an amorphous solid dispersion of 30 % (w/w) drug load for most of the APIs. Even for the very lipophilic APIs, such as cinnaconazole and telmisartan, amorphous dispersion of 15 – 20 % (w/w) drug load can be obtained. All extrudates with PVA show solubility enhancement compared with crystalline APIs. For example, an 80-fold solubility enhancement of itraconazole is observed during the real-time dissolution experiment (Figure 1). In addition, the study shows that 30 % itraconazole demonstrates an immediate drug release and achieves more than 80 % dissolution after 15 min.

To optimize the HME processing and the dissolution of APIs, spray-dried sorbitol or meglumine are added as plasticizers (Table 3). In the case of telmisartan, which has a very high melting point of 260 °C, the solubility can be improved with the addition of a plasticizer from 26 mg/mL (only PVA) to 39 mg/mL (PVA/megumine) or 52 mg/mL (PVA/sorbitol) (Figure 2). Even a thermosensitive API, such as ibuprofen (T<sub>mel</sub> = 75 – 78 °C), can be extruded with PVA and 17.5 % meglumine as a plasticizer into a stable solid dispersion system with a minimum 30 % (w/w) drug loading and a 2-fold solubility enhancement. Therefore, it is assumed that plasticizers can optimize the HME processing based on PVA, especially for the APIs which have a very high melting point or very low melting temperature.

Results
Thermal analysis (TGA) indicated that the PVA used in this study is non-degradable up to 250 °C (Table 1), allowing applications over a wide temperature range. This study showed that various model APIs could be formulated into stable, amorphous, solid dispersion of 15 – 50 % (w/w) drug load (Table 2) using PVA in hot melt extrusion.

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

References