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 % for 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 thermo-properties were selected (Tables 2 and 3). Polyvinyl alcohol (Parteck® MXP, MilliporeSigma) with an 87 – 89 % hydrolysis grade, MW approx. 32,000 Da was selected as the thermoplastic polymer. Sorbitol (Parteck® 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 homogeneously 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 used. The obtained extrudate was cryo-micronized into fine particles (D^{50} = 100 – 120 µm) and then analyzed using DSC (crystallinity) and HPLC (content); real-time dissolution analysis was done with a Sotax AT 7 system (Aesch, Switzerland). For the API stability assay, the milled extrudate was stored under different conditions (25 °C/60 % r.H.; 40 °C/ 75 % r.H.; 2 – 4 °C) for a maximum of 12 months.

Results

Thermal analysis (TGA) indicated that the PVA used in this study was thermostable up to 250 °C (Table 1), allowing for 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.

T_g (by DSC)	40 – 45 °C
T_m (by DSC)	170 °C
T_{deg} (by TGA)	≥250 °C
Melt viscosity (D=200 s^{-1})	345.3±7.8 Pa·s
Melt viscosity (D=1200 s^{-1})	174.0±1.7 Pa·s
Moisture before drying	1.68 %
Moisture after drying (105 °C/3 h)	0.06 %

Table 1: Physical properties of polyvinyl alcohol for extrusion processing

Compound	T_m of API	API Loading	Solubility Enhancement
Cinnarizine	122 °C	20 %	10-fold
Indomethacin	151 °C	30 – 50 %	3-fold
Ketoconazole	146 °C	30 %	17-fold
Naproxen	152 °C	30 %	3.5-fold
Atorvastatin	160 °C	30 %	135-fold
Itraconazole	167 °C	30 %	80-fold
Telmisartan	260 °C	15 %	6-fold

Table 2: List of APIs and their performances with PVA as HME matrix polymer

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 cinnarizine 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). Moreover, the extrudate containing 30 % itraconazole demonstrates an immediate drug release and achieves more that 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/L (only PVA) to 39 mg/L (PVA/meglumine) or 52 mg/L (PVA/sorbitol) (Figure 2). Even a thermosensitive API, such as ibuprofen (T_m = 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.

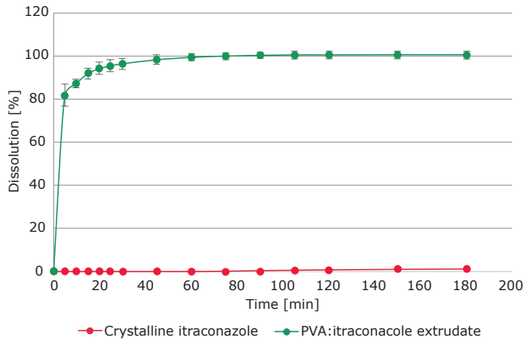

Figure 1: Dissolution of PVA/itraconazole extrudate in powder form (according to USP, non-sink condition, 900 mL SGF, 100 mg itraconazole)

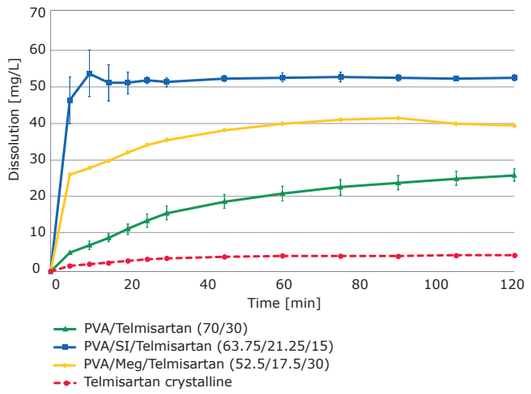

Figure 2: Dissolution performance of PVA/telmisartan extrudate with meglumine (Meg, 17.5 %) or sorbitol (SI, 21.25 %) as plasticizer (according to USP, non-sink condition, 900 mL SGF, 100 mg itraconazole)

API BCS II	T_m of API	API Loading	Solubility Enhancement
Ibuprofen[1]	78 °C	30 – 40 %	2-fold
Naproxen[1]	152 °C	30 %	4.3-fold
Telmisartan[1]	260 °C	15 %	35-fold
Telmisartan[2]	260 °C	15 %	12-fold
Atorvastatin[2]	160 °C	30 %	154-fold

Table 3: HME performance of APIs using 75 % PVA and 25 % plasticizers ([1]meglumine, [2]sorbitol)

References
1. Kerns, E. H. High throughput physicochemical profiling for drug discovery. J Pharm Sci 2001; 90(11):1838-58
2. Shah, S.; Maddineni, S.; Lu, J.; Repka, M. A. Melt extrusion with poorly soluble drugs. International Journal of Pharmaceutics 453 (2013) 233–25

The stability of the milled extrudate with itraconazole as model drug is confirmed at different storage conditions over 12 months. Amorphous state analyzed with DSC (data not shown), API content confirmed with HPLC (Table 4) and dissolution performance (Figure 3) do not show any changes during storage.

Sample	API content [%], n=2
Extrudate t=0	30.0
Extrudate t=12 M, 2 – 4 °C	30.0
Extrudate t=12 M, 25 °C, 60 % r.H.	28.6
Extrudate t=12 M, 40 °C, 75 % r.H.	28.1

Table 4: Itraconazole content of extrudate after preparation (t=0) and after 12 months storage at 2 – 4 °C, 25 °C/60 % r.H., and 40 C/75 % r.H.

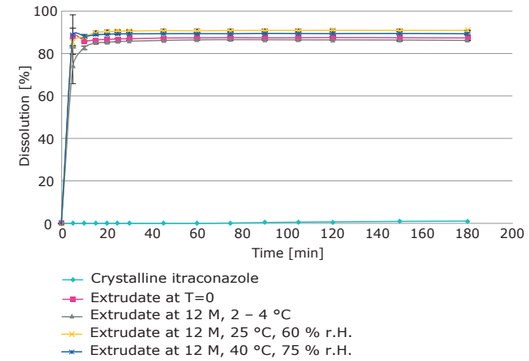

Figure 3: Dissolution performance of PVA/itraconazole extrudate after 12 months storage at 2 – 4 °C, 25 °C/60 % r.H., and 40° C/75 % r.H.

Summary

The study demonstrates that pharmaceutical-grade PVA can be used as a thermoplastic and thermostable polymer for HME to achieve a stable solid dispersion of a poorly water-soluble API with significantly improved solubility. Furthermore, PVA shows additional benefits regarding HME technology, such as high drug loading up to 50 %, excellent thermostability during the HME processing and stability of extrudate at accelerated conditions.

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