Solubility enhancement via amorphous solid dispersions: Extended functionality by applying a versatile polyvinyl alcohol platform for hot melt extrusion

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Purpose

The limited number of available polymers for hot melt extrusion is a challenge for formulators. Often the development focus is laid only on ASD stability. Novel ASD formulations are also targeting an enhanced functionality by the integration of additional polymers or surfactants.[1]

Objectives

Development of a broad polymer platform, based on polyvinyl alcohol (PVA).

Understand the impact of molecular design of PVA on the performance of the polymer for the creation of amorphous solid dispersions.

Methods

Melt Rheology

Thermo-Fisher Scientific Haake Mars Rheo 60 (Thermo Fisher Scientific, Waltham, USA) temperature ramp from 170 °C to 230 °C (3-82)/250 °C (4-88) ΔT/t=2 °/min oscillating Controlled Deformation, CD, γ_0=0.1%, f=1.0 Hz Gap=1 mm, plate-plate geometry 25 mm diameter

Dissolution

pH-shift method (750 mL 0.1M HCl for 120 Min, add 250 mL PP pH 6.8 final 1,000 mL) HME formulation 20% drug load; Paddle; 50 rpm; total runtime 300 Min, n=3 via HPLC measurement.

Hot Melt Extrusion

Pharma 11 (Thermo Fisher Scientific, Waltham, USA)
Die: 2 mm; Screw configuration containing three kneading elements
Gravimetric feeding: Congrav OP1-S, downstream, via conveyor belt (Brabender GmbH, Duisburg, Germany)

Differential Scanning Calorimetry

DSC 3+ (Mettler Toledo, USA)
sample mass ≈ 5 mg, n=3, 40µl Al-pan

1. 1st heating cycle -20 °C to 210 °C
2. isothermal at 210,0 °C, 3,00 min,
3. cooling cycle 210 °C to -20 °C,
4. isothermal at -20,0 °C, 3,00 min,
5. 2nd heating cycle -20 °C to 250°C

50 ml/min N2, heating/cooling rate 5 K/min,
data evaluated with STARe-Excellence Software

Results

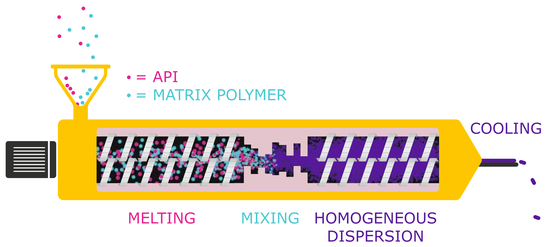

Figure 1.
Simplified schematic view of the Hot Melt Extrusion (HME) process, visualizing the transition of API and matrix polymer from feeder to the extruder die.

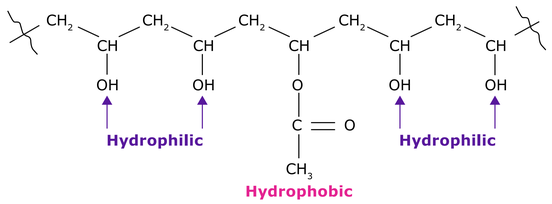

Figure 2.
Chemical structure of a partially hydrolyzed PVA.

PVA 3-82 and 4-88 are thermostable polymer designed for HME.

- The first number specifies the apparent viscosity in mPas of a 4% aqueous solution at 20 °C which is also linked to the relative molecular weight of the polymer chain.
- The second number represents the degree of hydrolysis of the polyvinyl acetate (Fig. 2).

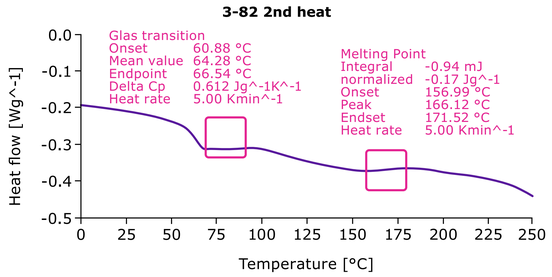

Figure 3.
DSC profiles of MXP 3-82 and MXP 4-88. A higher hydrolysis grades show a shift of thermal events to higher temperatures which correlates with rheological behavior.

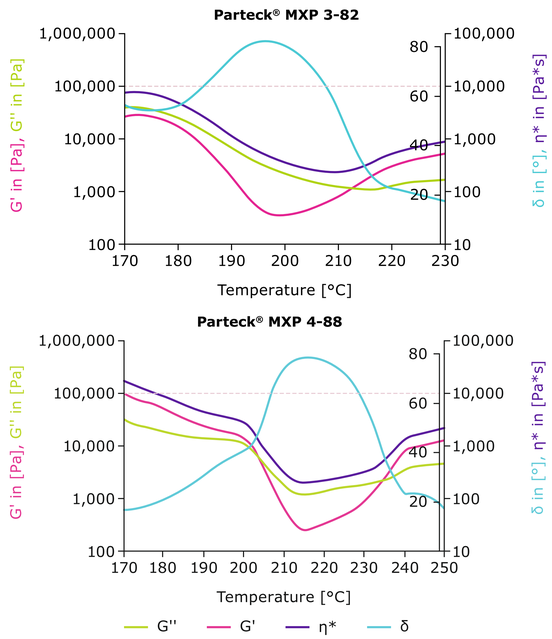

Figure 4.
Melt viscosity data for Parteck® MXP 3-82 and Parteck® MXP 4-88 indicating a broad processing range.

Melt rheology of both PVA 3-82 and 4-88 showed a significant difference in crossover points as well as the expectable process window. While the viscosity of PVA 4-88 remains quite high until a temperature of ~200 °C and G' (storage modulus) remains the dominant modulus, a crossover of G' and G''(Loss modulus) can be observed at 203 °C within a significant drop in melt viscosity. A second crossover of G'' and G' along with a decreasing phase angle δ indicates the begin of polymer degradation at around 235 °C. In contrast, MXP 3-82 G'' is already the prominent modulus over G' at 170 °C, along with a constant decrease of melt viscosity when increasing the melt temperature. At around 212 °C a G''/G' crossover as well the drop of phase angle δ indicates a beginning degradation of the polymer melt. The observed rheological behavior of both polymers indicated that extrusion range in terms of barrel temperature as well as torque is lower for 3-82 then for 4-88. Several conducted HME trials both with 3-82 and 4-88 proved that the process range of 3-82 is feasible at 130–210 °C* and 150–230 °C* for 4-88, which correlates to the rheological data generated (see Fig. 4).

*incl. addition of plasticizer

Parteck® MXP 3-82		
Media	**pH**	**Solubility at 37 °C (mg/mL)**
SGF_sp	2	272.8
0.1M HCl	1	67.9
Acetate buffer	4.5	67.1
FaSSIF	6.5	60.9
PBS	6.8	57.45
PBS	7.4	215
Parteck® MXP 4-88		
Media	**pH**	**Solubility at 37 °C (mg/mL)**
SGF_sp	2	199.2
0.1M HCl	1	51.55
Acetate buffer	4.5	257.6
FaSSIF	6.5	55.25
PBS	6.8	54.8
PBS	7.4	215

Table 1.
Solubilities of both 3-82 and 4-88 in different dissolution media.

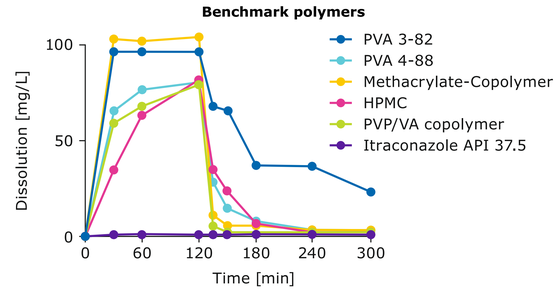

Figure 6.
Dissolution data of drug loaded extruded matrices; assessment via pH shift.

The dissolution data shows for a low hydrolysis grade outstanding supersaturation performance after shifting the pH from gastric to intestinal fluid conditions which is useful for hydrophobic API´s like itraconazole as model compound.

Conclusions

For PVA based polymers the hydrolysis degree is impacting the process temperature range and thermal behavior (Fig. 3 & 4). The chance in amphiphilic structure is also affecting the solubility in relevant media (see Table 1). Higher hydrolyzed PVAs show a superior temperature tolerance, whereas low hydrolyzed PVA can be utilized at lower process temperature and prove to be very effective in prolongating the supersaturated state of low soluble drug substances (Fig. 6).

References

1. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharmaceutica Sinica B. 2021;11(8):2505-36.

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