

Interaction of thermal and rheological parameters critical for the processability of polyvinyl alcohol-based systems during hot melt extrusion

Florian Hess^{1,2}, Thomas Kipping¹, Werner Weitschies², Julius Krause²



Purpose

Hot melt extrusion (HME) is a pivotal pharmaceutical manufacturing process employed to enhance the bio-availability of poorly soluble active pharmaceutical ingredients (APIs) in oral dosage forms.

Often the applicability of the process is limited by the melt viscosity. The upper limit is considered at about 10,000 Pas.³

Especially for high melting polymers it is of particular interest to explore concepts that can widen the process range.

Objectives

Identify suitable plasticizers in combination with polyvinyl alcohol (PVA) grades and investigate their influence on the melt viscosity. The aim is to assess correlations between thermal characteristics and key rheological parameters.

Methods

Materials

Polyvinyl alcohol (PVA, Parateck[®] MXP 3-82 and 4-88), glycerol (GLY), triacetin (TRI), triethylcitrate (TEC), polyethylene glycol (PEG 300), mannitol (MAN, Parateck[®] M200) and sorbitol (SOR, Parateck[®] Si150), from Millipore Sigma (Darmstadt Germany), plasticizer content at 10 wt%.

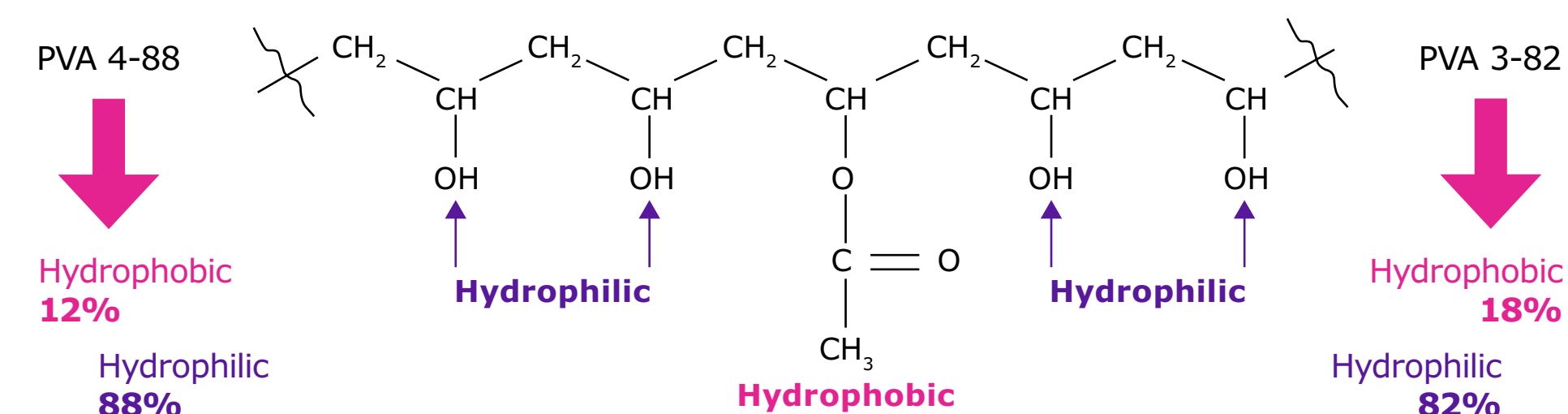
Melt rheology

Haake[™] Mars[™] Rheo 60 (ThermoFisher Scientific, USA). Plate diameter = 25 mm, gap = 1 mm, sample mass ≈550 mg, viscosity and phase angle delta, were determined from 170 °C to 250 °C for PVA 4-88 blends, and from 150 °C to 230 °C for the PVA 3-82 blends, 2K/min, $\gamma_0 = 0.1\%$, $f = 6.28$ rad/s, $n = 3$.

Differential scanning calorimetry (DSC)

DSC 3+ (Mettler Toledo, USA) sample mass ≈5 mg, $n=3$, 1st heating cycle -80 °C to 210 °C, cooling cycle 210 °C to -80 °C, 2nd heating cycle -80 °C to 250 °C 10 K/min, 50 mL/min N₂, 40 µl Al crucible, data evaluated with STARe-Excellence Software.

Results



- The initial digit indicates the apparent viscosity of a 4% water-based solution at 20 °C, measured in mPas. It is correlated with the relative molecular weight of the polymer chain.
- The second digit stand for the proportion of acetate groups on the PVA backbone that have been converted to hydroxyl groups.⁴

Rheological analysis

Viscosity

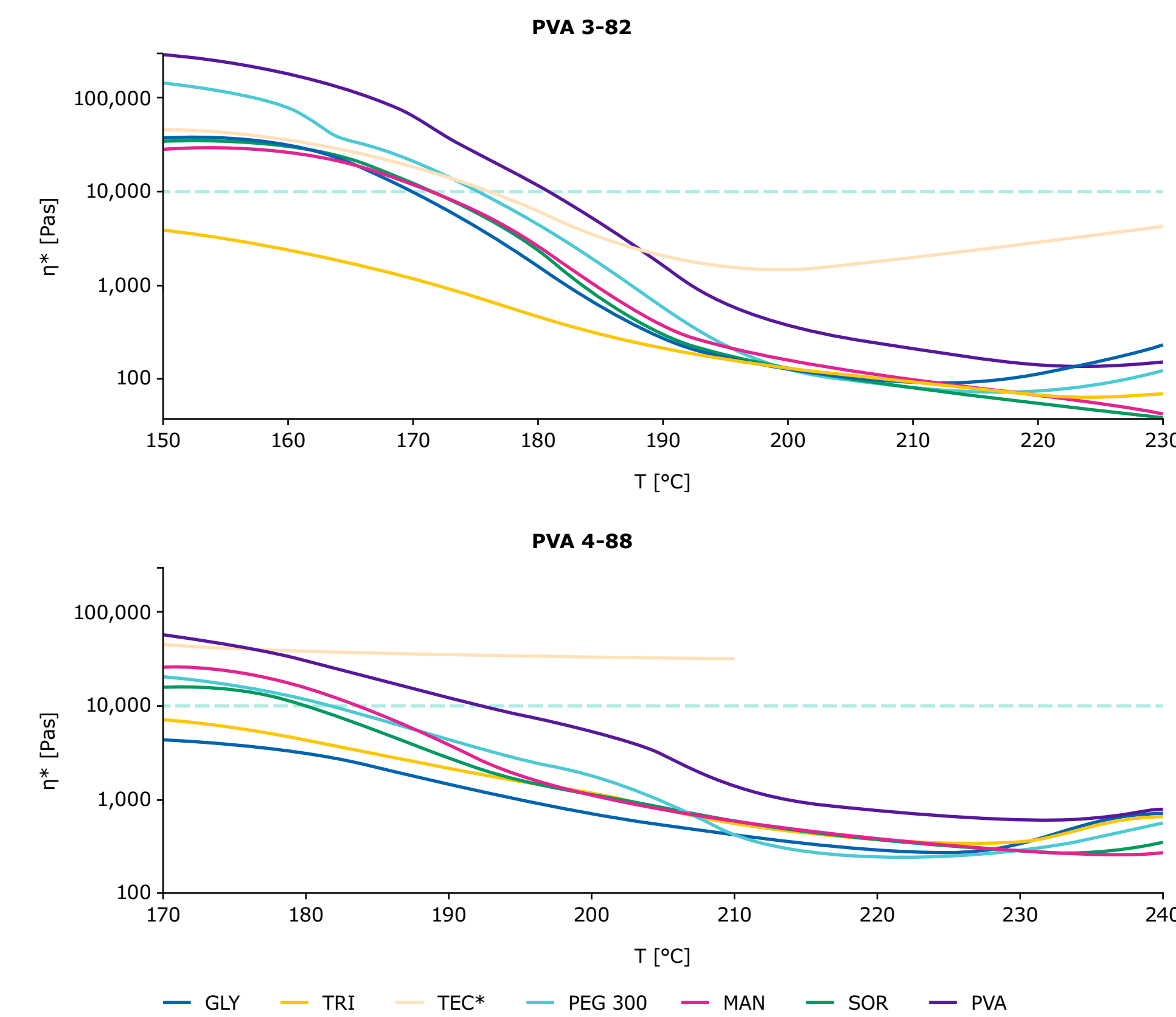


Figure 1. Complex viscosity against temperature: left: PVA 3-82 and PVA 3-82/plasticizer systems; right: PVA 4-88 and PVA 4-88/plasticizer systems, mean of $n=3$.

- The two PVA grades demonstrated varying process windows. For PVA 3-82, the theoretical beginning of the processability is approx. at 180 °C, which is about 10 degrees lower than the starting point for PVA 4-88.
- Different plasticizer combinations could extend these process windows even further:
 - PVA 3-82 could already be processed below 150 °C in combination with triacetin.
 - For PVA 4-88, the starting point of workability could be lowered to below 170 °C by adding glycerol or triacetin.
 - Triethyl citrate exhibited decomposition signs with PVA 4-88 (starting at 210 °C), with PVA 3-82 TEC displayed no signs of decomposition, but it increased the viscosity of the pure PVA from 190 °C onwards.

plasticizer	PVA 3-82		PVA 4-88	
	Tg [°C]	Tm [°C]	Tg [°C]	Tm [°C]
none	62.6	170.3	67.3	176.7
Gly	38.2	150.3	44.3	166.2
TRI	56.3	129.4	61.9	148.5
TEC	61.5	155.1	70.7	133.4
PEG 300	44.0	174.0	48.8	178.6
MAN	52.1	157.1	53.3	168.4
SOR	49.9	153.9	50.3	166.9

Table 1. Thermal evaluation of binary systems; DSC measurements mean of $n=3$ second heating cycle.

DSC measurements

- The plasticizer combinations with glycerol and peg lowered the glass transition temperature the most for both PVA grades.
- Triacetin lowered the melting point of PVA 3-82 the most.
- Triethylcitrate lowered the melting point of PVA 4-88 the most, Triacetin had the second highest effect on PVA 4-88.

Visco-elastic behavior

- Besides viscosity, visco-elastic behavior plays an important role in hot melt extrusion. A predominantly viscous behavior is desired, characterized by a phase angle above 45°.⁵
- Triacetin and glycerol increased the ideal viscoelastic range the most.
- The polyols mannitol and sorbitol seem to have a temperature stabilizing effect on the PVA 3-82. This could allow for a further expansion of the process window.
- TEC showed a reversed rheological behavior for both polymers, predominantly elastic properties were observed.

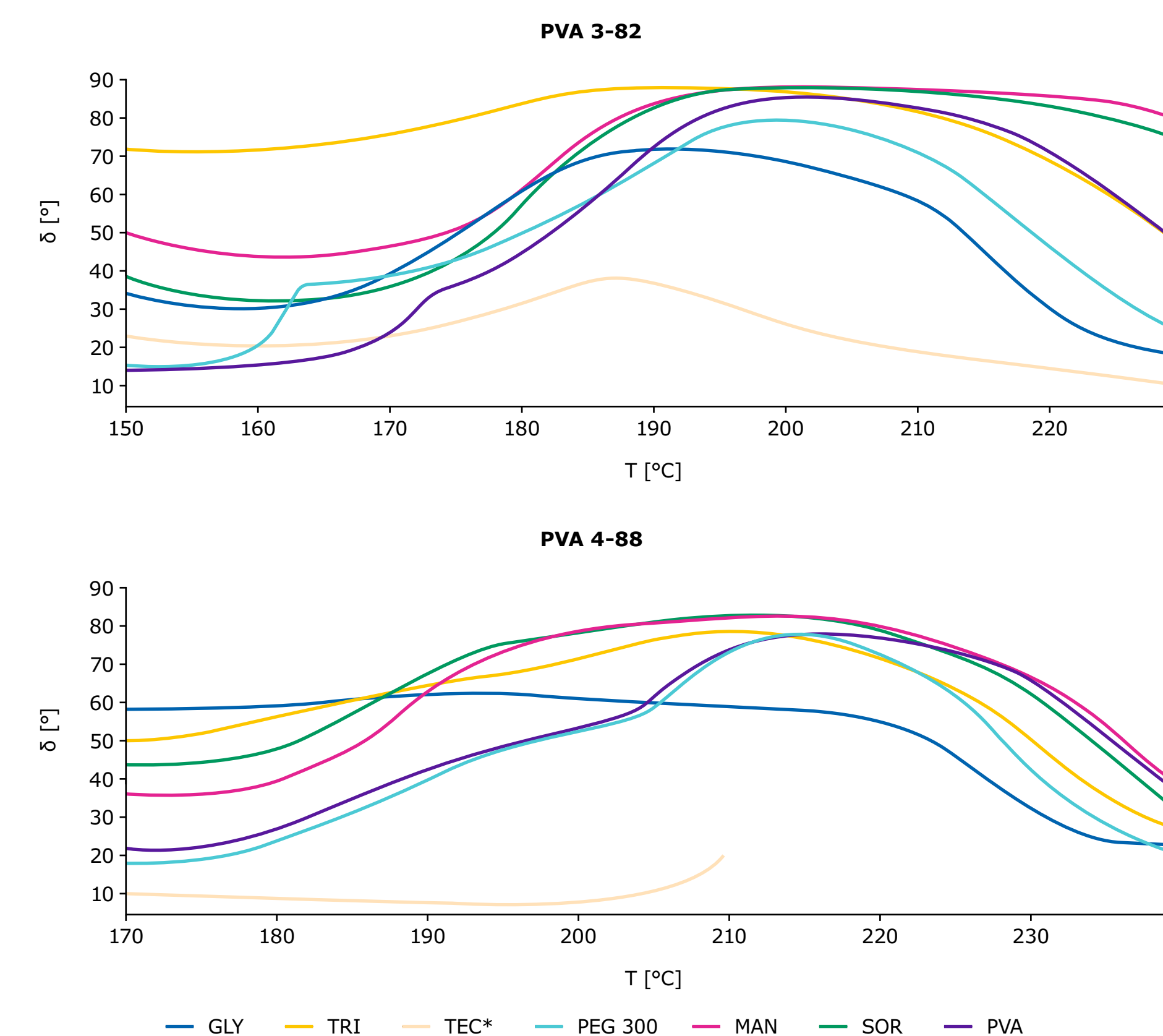


Figure 2. Phase angle δ against temperature left: PVA 3-82 and PVA 3-82/plasticizer systems; right: PVA 4-88 and PVA 4-88/plasticizer systems, mean of $n=3$.

Conclusions

Suitable plasticizers for melt extrusion with PVA were identified and ranked in terms of their influence on viscosity of the melt (Fig 3.). Combinations could be identified that increase the temperature range at which the polymers can be processed or shift it to a lower temperature. This may be a new approach for formulating temperature sensitive active pharmaceutical ingredients. Moreover, a correlation between the preliminary thermal analysis and the viscous behavior of the binary systems in the melt was observed. A decrease of the binary systems meltpoint correlates in most cases with the decrease in viscosity.

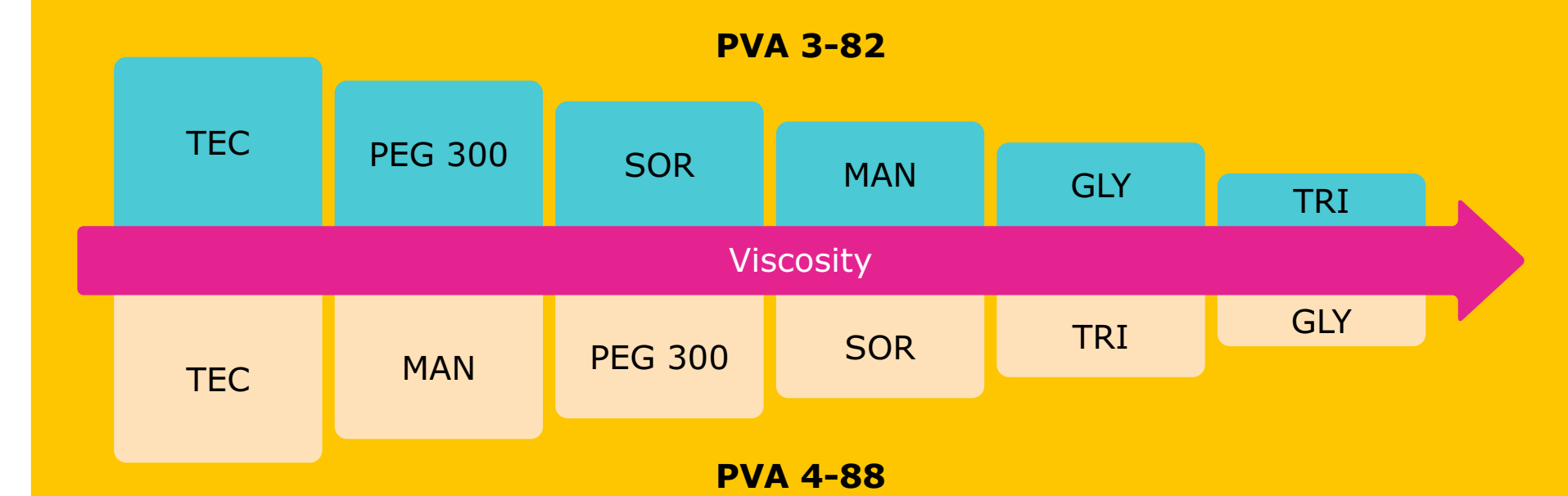


Figure 3. Ranking of viscosity lowering effects. Increasing from left to right.

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Contact details: thomas.kipping@emdgroup.com

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