Understanding the stabilization mechanism of polyvinyl alcohols (Parteck® MXP) in ASDs by structure-related properties and PC-SAFT modeling

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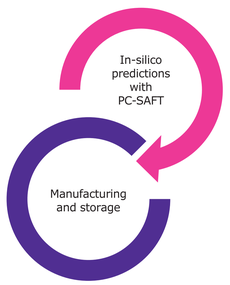
Purpose

- For the development of amorphous solid dispersions (ASDs), the physical stability of the formulation is a key challenge determining their performance additional to dissolution and solubility.
- Selecting the right polymer/API combination early on is crucial for proper CMC development.
- In this work, a thermodynamic modelling approach (PCSAFT)[1,2] is utilized to predict API/polymer compatibility leveraging the potential to reduce experimental screening efforts.

Objectives

- Generate a PC-SAFT model for semi-crystalline polymer polyvinyl alcohol (PVA – Parteck® MXP).
- Calculate ASD phase diagrams of PVA and various model APIs (indomethacin (IND), naproxen (NAP) and itraconazole (ITR)) and validate predictions.
- Calculate PC-SAFT activity coefficients to enable API/PVA compatibility predictions, thus providing an intermolecular interaction-based assessment of beneficial API/PVA combinations.

Methods



- API crystallization and miscibility
- Predictive interaction screening for many APIs
- Model for semi-crystalline polymer Parteck® MXP 4-88
- Validation of predicted phase diagrams via differential scanning calorimetry (DSC)
- Hot-melt extrusion and storage
- Crystallinity detection via X-ray and DSC

Results

- Extension of PC-SAFT approach to hot-melt extruded solid dispersions containing semi-crystalline polymer PVA (Parteck® MXP) as carrier matrix.
- Model assumptions for semi-crystalline polymer:
  - API solely dissolves in the amorphous parts of the polymer (66 w%): amorphous vinyl acetate (Vac)/ vinyl alcohol (VA) ratio is 68/32 w%
  - Crystalline VA polymer fractions are considered unavailable for API interactions (34 w%)

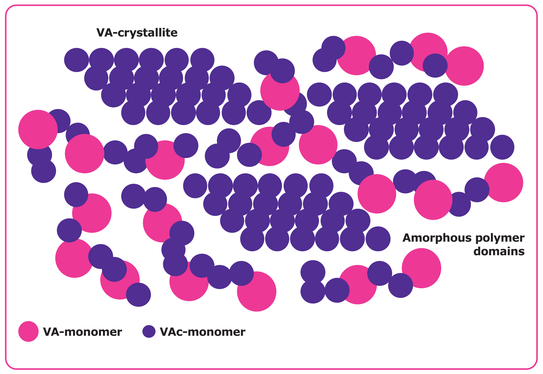


Figure 1.
Scheme of the semi-crystalline PVA polymer exhibiting crystalline domains being unavailable for API interactions and amorphous domains interacting with enclosed APIs.

API	GFA class	T_m/°C	T_g/°C	Max. stable DL in Parteck® MXP	Ref.
IND	3	161	45	30 wt%	5
NAP	1	153	-3	10 wt%	6
ITR	3	168	58	10 wt%	5

Table 1.
Physical properties of the investigated APIs and the maximal observed stable drug load (DL) during stability studies (remained amorphous for investigated period of time).

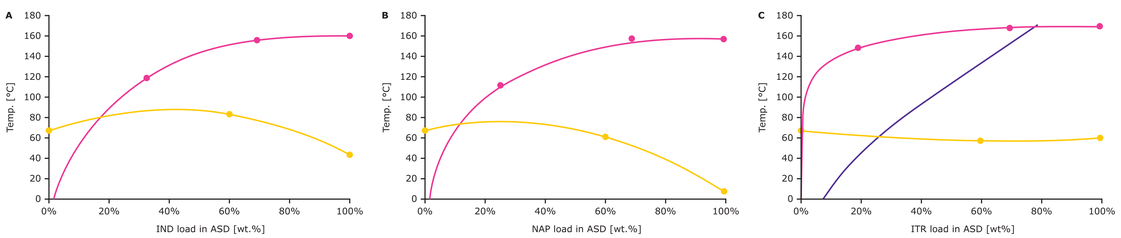


Figure 2.
Modeled API/PVA4-88 phase diagrams of **(A)** IND/PVA4-88, **(B)** NAP/PVA4-88 and **(C)** ITR/PVA4-88 containing the PC-SAFT modeled crystalline solubility in amorphous PVA4-88 (magenta line) and the Kwei modeled glass-transition temperature (yellow line) as well as the predicted miscibility gap between PVA4-88 and ITR (purple). Symbols are experimental data points obtained from DSC measurements.

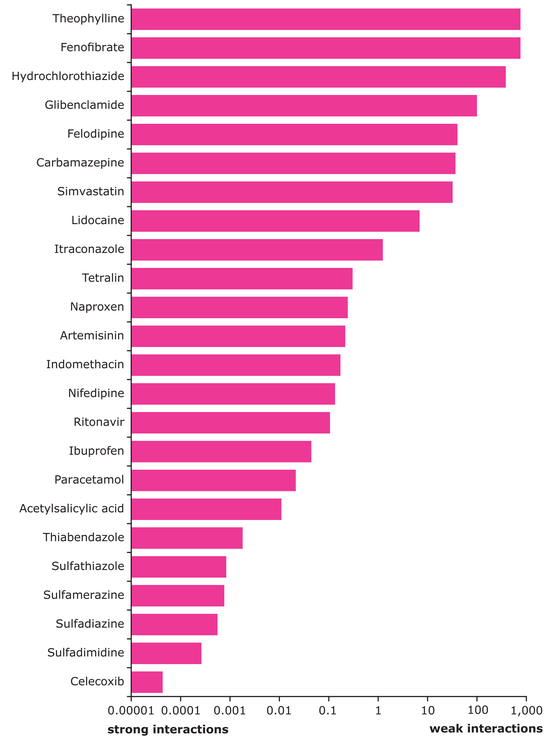


Figure 3.
Via PC-SAFT predicted API/PVA4-88 activities in 20 wt% ASDs at 25 °C. Low values represent strong interactions and high ASD stabilization potential, high values represent weak interactions and low ASD stabilization potential.

- Phase diagrams of IND/PVA and NAP/PVA appear very similar showing a maximum for T_g indicating strong API/polymer interactions.
- NAP/PVA: T_g is significantly decreased at higher drug loadings reflecting the lower GFA (glass-forming ability) and low kinetic stabilization potential of pure amorphous NAP.
- ITR/PVA: immiscibility predicted above 12 w%, the new evolving amorphous phase contains 99.9 w% ITR.
- Calculations were confirmed by experimental data: GFA, highest drug load (DL) in PVA and physical stability.
- These calculations are full predictions and require no additional experimental data, they thus serve as screening tool for early formulation development.
- Compounds exhibiting aromatic nitrogen acceptor functional groups show stronger interactions with PVA, likely due to the formation of the strong OH···N hetero synthon.[4]

Conclusions

- Successful extension of PC-SAFT approach to the semicrystalline polymer PVA (Parteck® MXP).
- Parteck® MXP shows stabilizing properties most likely due to interactions of the hydroxyl groups with hydrogen bonding acceptor moieties of the APIs.
- PC-SAFT was utilized as a screening tool for API/polymer compatibility.
- With Parteck® MXP good stabilizable API candidates are predictable.
- In future: validation interaction screenings with ssNMR to experimentally confirm the stabilization mechanism.
- In future: assess the impact of varying hydrolysis degree on stabilization potential.

References

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