M1030-07-39

# DAYS OR CENTURIES?
# PREDICTING THE SHELF-LIFE OF ASDS


**Christian Luebbert, Gabriele Sadowski**
**amofor GmbH**

**amofor GmbH, Otto-Hahn-Str. 15, 44227 Dortmund, Germany**
**Contact: luebbert@amofor.de**


aaps PharmSci 360

## PURPOSE

Amorphous solid dispersions (ASDs) are a state-of-the-art enabling formulation technique for poorly water-soluble drugs.

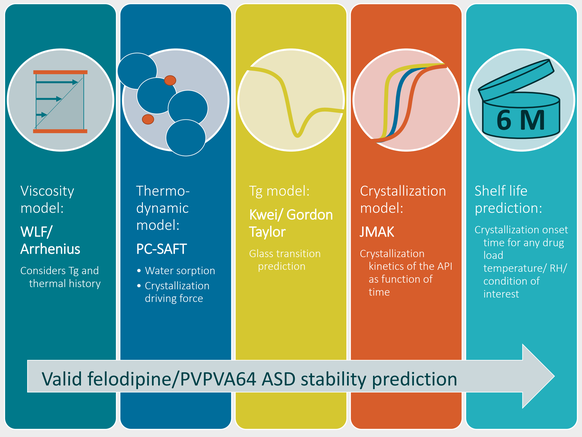
Drug recrystallization in the polymer matrix highly unwanted: marks end of shelf life of such a formulation.

- Overcoming the poorly understood drug recrystallization risk during storage and random stability screenings
- Understanding the impact of different storage conditions (temperature, RH) and packaging alternatives
- Predicting shelf life at any drug load/ temperature/humidity condition ahead of the stability test with novel in-silico tool and minimal data set

## OBJECTIVE

Develop and validate **predictive model for shelf life** considering thermodynamic factors (water absorption, fundamental crystallization driving forces), kinetic factors (glass transition, diffusivity in the ASD), drug-specific crystallization mechanism (nucleation, crystal growth, glass-forming ability), thermal history (spray drying, melt extrusion, glass aging) and their mutual impact.

## METHODS

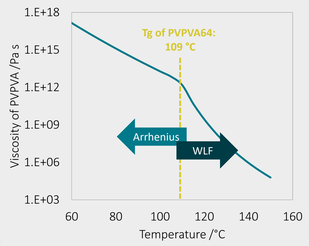



## RESULTS

### Viscosity model for the ASD matrix

*Understanding kinetic factors of ASD shelf life*

- Diffusivity within ASD matrix governed by polymer viscosity
- PVPVA64 viscosity above Tg obtained from literature
- Time/ Temperature Superposition principle: Only Tg of ASD required to determine ASD viscosity
- Analogous principle applied to wet Tg/viscosity at elevated RH

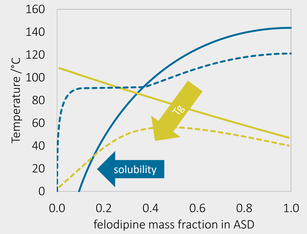



*Temperature dependent viscosity of PVPVA64.*

### Thermodynamic model PC-SAFT

*Understanding thermodynamic factors of ASD shelf life*

- Equilibrium felodipine solubility in PVPVA64, felodipine crystallization driving force, moisture sorption and the mutual impact predicted (PC-SAFT)
- Equilibrium solubility dramatically reduced at room temperature

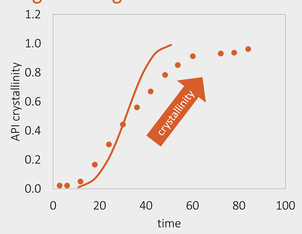



*PC-SAFT predicted felodipine/PVPVA64 phase diagram (solubility: blue, Tg: yellow) at 0% RH (solid) and 75% RH (dashed).*

### Crystallization model

Understanding nucleation and crystal growth regime

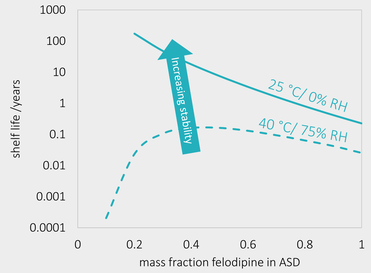
- Measuring crystallization kinetics in pure felodipine or high felodipine loaded ASDs at high T/RH conditions
- Crystallization kinetics measured in
  - pure API and/or at
  - High API load and/or at
  - High T/RH




*Schematic crystallization of a pure API and JMAK modeled crystallization as function of time.*

### Stability prediction – days or centuries?

Felodipine/PVPVA64 ASD stability at moderate storage conditions predicted as function of felodipine load in ASD:

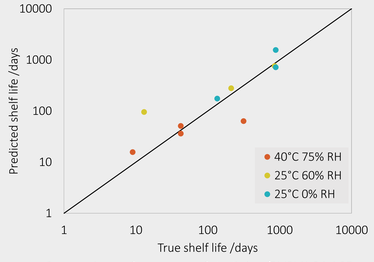



*Predicted shelf life of felodipine/PVPVA64 ASDs at 25C/ 0% RH (solid) and 40C/ 75% RH (dashed).*

The predicted shelf life ranges from few days at 40C/ 75% RH (max. 0.16 years at 40w% felodipine load) to centuries at 25C/0% RH (172 years at 20wt% felodipine load and 25C /0% RH)

### Validation of the in-silico tool

- Long-term storage of spray-dried ASDs with felodipine content between 10w% and 90 w% at the storage conditions 25C / 0% RH, 25C/ 60% RH and 40C/ 75% RH for three years
- Crystallization onset time determined via repeated X-ray diffraction analysis




*Comparison of measured felodipine/PVPVA64 ASD shelf life (crystallization onset) to predicted shelf life.*

## CONCLUSIONS

- Novel in-silico model has been successfully applied for predicting the shelf life of metastable ASDs
- Shelf-life predictions validated by three-years stability tests at three storage conditions
- Revolutionary risk assessment of storage test results at early stage of formulation development, before conducting the tests
- Few key experiments instead of random screenings
- Stability data collected at so-called 'accelerated', harsh storage conditions within short time do not at all reflect the shelf-life at moderate storage conditions as thermodynamic and kinetic aspects differ completely
  - ➢ The developed model can extrapolate 'harsh data' better as it accounts for the changes in thermodynamic and kinetic aspects
- High flexibility with respect to potential data input and output
- Predict the shelf life for any analytical level of detection (XRD e.g., 3% crystallinity vs. 1% crystallinity in DSC)

## MINIMAL REQUIRED DATA INPUT

- Thermodynamic model: 5 solubilities in different organic solvents + 1 DSC or DVS of the ASD (phase diagram validation) + 1 DSC of the pure API ($T_g$, melting temperature and -enthalpy)
- Kinetic model: GFA class of the API or crystallization kinetics at harsh condition (1 DSC or DVS)
- ➢ Only 8 simple measurements + in-silico tool required for ASD shelf-life prediction