Faculty of Pharmaceutical Sciences

The Influence of Solvent Evaporation Rate on the Physical Stability of Solid Dispersion – A Fast Screening Approach

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Potentials of solid dispersion

Advantages:

- Drug molecularly dispersed in polymer matrix leading to maximum specific surface area
- Drug is amorphous dispersed in polymer matrix leading to increased drug solubility upon dissolution
- Dispersion of drug within polymer leads to increased wettability during release

Challenges:

- Risk of recrystallization of amorphous drug
- Many formulation and process parameters influence on amorphous drug stability in solid dispersion.
- Poor understanding of factor relationships influencing on drug stability.
- With many formulation parameters and process factors, there is a need for development of a flexible high throughput screening platform, which allows quick screening of solid dispersion stability.

Formulation and preparation of solid dispersions

- The use of solvent evaporation method in preparing solid dispersions is often used by many studies. However, the evaporation methods employed ranged from:
  - Rotary evaporation
  - Evaporation under a stream of nitrogen
  - Evaporation on hot plate
  - Spray drying

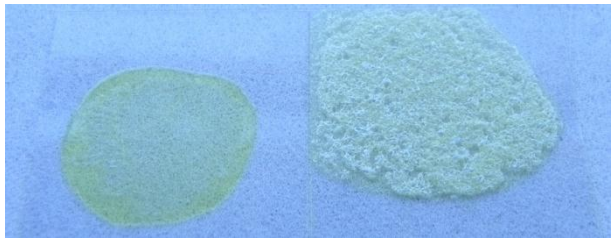
- The solvent evaporation rate is in many cases uncontrolled, and often unknown.

- Even though there is a lively scientific knowledge exchange and inter-study comparison of solid dispersion stability when formulation parameters are varied, the use of processing parameters to obtain such formulations are often not considered.

The basis of a platform with high-througput potential

- Piroxicam (PX) and polyvinylpyrrolidone (PVP) dissovled in acetone and methanol. A fixed volume of solvent is transferred to a glass plate where temperature on glass plate surface can be accurately controlled, and solvent evaporated under constant temperature.

- Prepared solid dispersions are monitored using polarised light microscopy (PLM), and images obtained are analysed using in-house developed Matlab routine. The monitored responses are numbers of crystalline spots on image, and the total percentage area coverage covered by these spots on image.



Left and right images show solid dispersions evaporated at 30 and 70C respectively

Establishment of experimental design

Using the aforementioned screening platform, 3 factors are investigated:

1) Evaporation temperature
2) PX:PVP ratio
3) PVP molecular weight

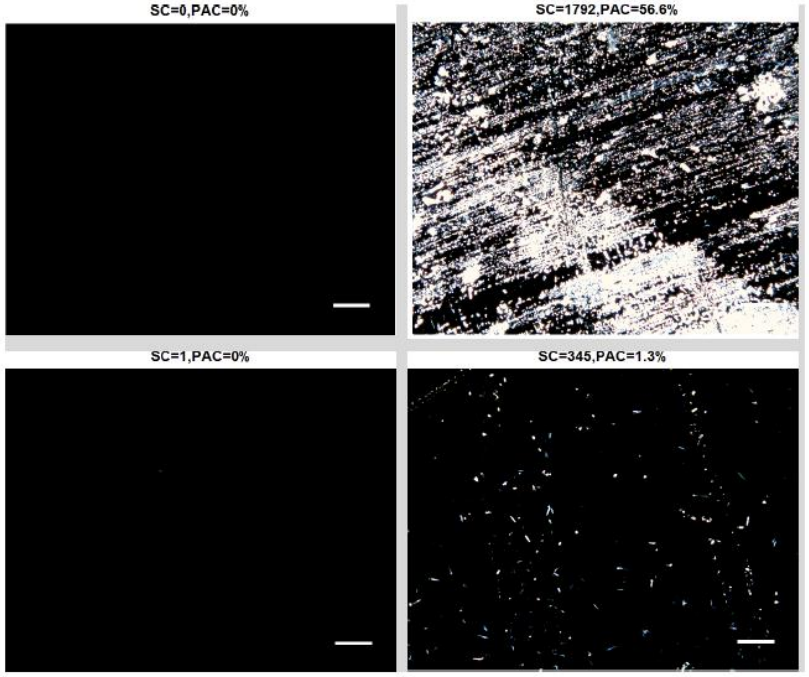
Samples are monitored using PLM, and 2 images are obtained at the center of samples at day 0, 10, 20 and 30

Table 1: Overview of the factors employed for the experimental design and the level each factor is varied.

Factors	Low level	Center point	High level
Evaporation temp.	30 °C	50 °C	70 °C
PX : PVP	1:1	1:2	1:3
PVP molecular weight	30000 MW	450000 MW	1000000 MW

Significance of evaporation temperature

A clear difference between PX:PVP 30000MW 1:1 evaporated at 30 C and 70 C at day 0 and day 30 is observed. The images below gives an impression of significance of evaporation temperature on physical drug stability.



Left: day0 right: day 30
Evaporation temperature 30C

Left: day0 right: day 30
Evaporation temperature 70C

Results from experimental design

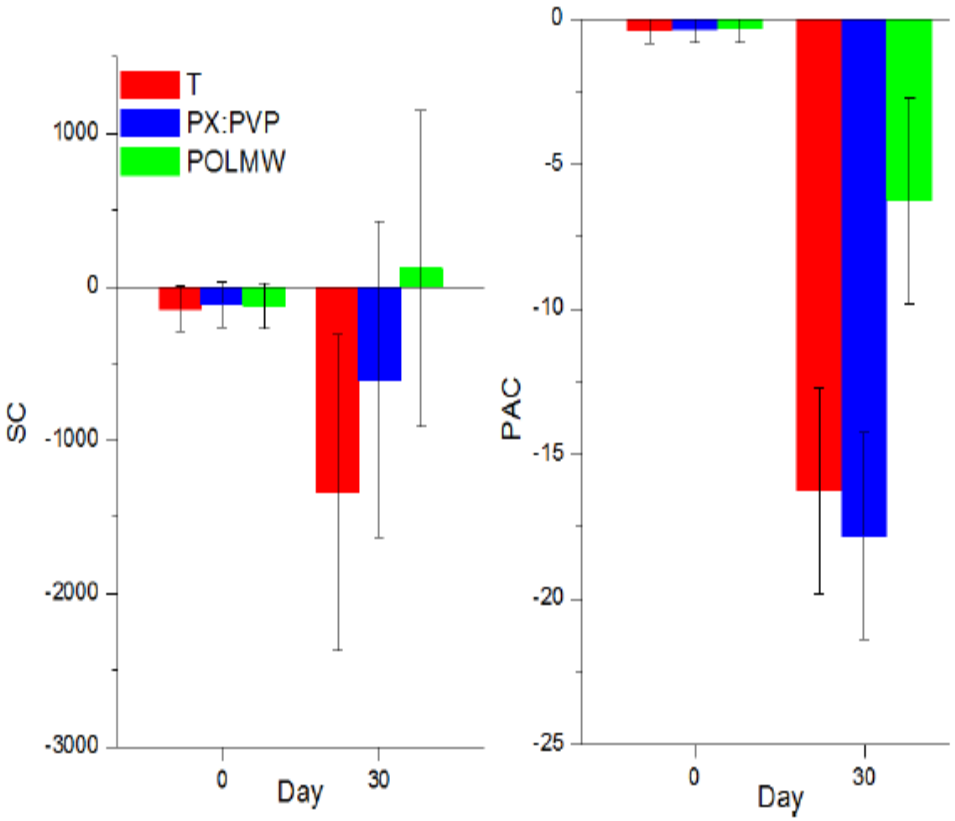


Figure 2: Effect plots from experimental design showing the effects of factors on the investigated responses. T: temperature, PX:PVP: piroxicam:PVP ratio, POLMW: PVP molecular weight.

Evaporation temperature accounts the largest effect in lowering spot count, which indicates the nucleation extent. This effect is followed by PX:PVP ratio accounting for second largest effect.

PX:PVP ratio accounts the largest effect in decreasing area coverage, which indicates the extent of crystal growth, while evaporation temperature accounts the second largest effect.

PVP molecular weight does not seem to influence nucleation rate, while it accounts a minor effect in decreasing crystal growth

Conclusion and future perspective

- PLM is a useful tool with non-destructive quantification ability in monitoring solid dispersions stability
- Evaporation temperature accounts the largest effect in inhibiting nucleation, while PX:PVP ratio accounts the largest effect in inhibiting crystal growth
- The effect of evaporation temperature and PX:PVP ratio is in the same order of magnitude in decreasing crystal growth

- Currently, our laboratory is investigating the suitability of the established platform in connection with other analytical techniques such as:
  - X-ray powder diffraction
  - FT-NIR microscopy
  - Raman microscopy
  - Interferens light microscopy
  - FT-IR spectroscopy

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