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Communication

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

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Abstract: Despite the promising potential of solid dispersions for increasing drug release rates, at present, the influence of many process and formulation parameters on solid dispersion stability is poorly understood. The present study utilizes polarized light microscopy and experimental design to compare the influence of three factors: solvent evaporation temperature, piroxicam (PX):PVP ratio and PVP molecular weight on solid dispersion physical stability. The results show that evaporation temperature accounts for the largest effect in inhibiting nucleation, while PX:PVP ratio accounts for the largest effect in decreasing crystal growth. The influence of increasing evaporation temperature and PX:PVP ratio are in the same order of magnitude in increasing physical stability of solid dispersions while PVP molecular weight only explains a minor effect in decreasing crystal growth of PX in PVP matrices.

Keywords: Solid dispersion, evaporation temperature, piroxicam, experimental design, polarized light microscopy, image analysis.

1. Introduction

There are several advantages of amorphous solid dispersion systems in relation to increase in drug release rate. A molecular dispersion of a drug in an amorphous polymer which decreases the drug particle size to an absolute minimum can be achieved, as well as formulations with improved wettability [1]. Despite the promising potential of solid dispersion systems, the physical stability of the amorphous drug is still an issue of concern. Many studies have focused on different formulation parameters affecting the physical stability in solid dispersions [2,3,4]. However, since physical stability is influenced by both formulation parameters and manufacturing process factors, a combined study estimating the effect of both on physical stability is needed.

In the early drug development phase where the available amount of drug compound is limited, small scale screening of solid dispersions can be useful in identifying the formulation parameters influencing drug stability. A screening study performed by Eerdenbrugh and Taylor shows the usefulness of polarized light microscope (PLM) to qualitatively distinguish the stability of drugs in different polymers [5]. Using PLM in screening solid dispersions has several benefits, which include the high resolution, high level of sample detail, short evaluation time and the nondestructive nature of the investigation. However, the main drawbacks of using PLM so far are related to its subjective data interpretation, and often it is difficult to obtain quantitative information from PLM images [2,5]. In the study from Eerdenbrugh and Taylor [5], the authors used discrete ranked responses to classify the amount of crystallinity in solid dispersions by assigning a class code to a given crystallinity level based on visual observation. Such responses cannot be interpolated onto an interval scale. For example the distance between "very poor" and "poor" does not necessarily equal to that between "good" and "excellent" [6].

Solvent evaporation is one of the main approaches for preparing solid dispersions [1]. However, studies utilizing this method differ widely in the evaporation methods, e.g. rotation evaporation [7,8], slow evaporation on a hot plate [9], evaporation under a stream of nitrogen [10] or spray drying [11]. In many cases the solvent evaporation rates between the methods are very different and the influence of evaporation rate on solid dispersion stability is unknown.

In the present study, a small scale solid dispersion screening platform with high throughput potential has been developed. The platform allows fast preparation of solid dispersion films on a preheated glass plate. Prepared formulations are subsequently screened using PLM, and the extent of drug crystallization is quantified using an in-house developed semi-automated image analysis routine. With piroxicam (PX) and polyvinylpyrrolidone (PVP) as model drug and model polymer respectively, the aim of the present study is to use experimental design in estimating the effect of three factors: evaporation temperature which dictates the evaporation rate, PX:PVP ratio and PVP molecular weight on the initial solid state form of PX in the solid dispersions and the physical stability of solid dispersions upon storage of up to one month.

2. Method

Materials

Piroxicam anhydrate (PX AH) was purchased from Chr. Olesen Pharmaceuticals, Denmark. Methanol and acetone were purchased from Lab-scan, Poland. Polyvinylpyrrolidone (PVP) K25, K64 and K90 were generously provided by BASF, Germany, with approximate molecular weights of 30000, 450000 and 1000000 respectively [12]. All materials obtained were of analytical grade, while PVPs were of technical grade.

Sample preparation

500 mg of PX AH was dissolved in 30 ml acetone, and 7 ml methanol was added. To this solution PVP was slowly added under magnetic stirring. To form the solid dispersion films a microscope cover glass with 0.15 mm thickness was placed on a hot plate (Krüss G12, Germany), with the temperature accurately controlled within $\pm 1^{o}$C. 60 µl of solvent was pipetted onto the glass surface and the solvent evaporated. The prepared solid dispersion films were stored in a desiccator over a saturated magnesium nitrate solution at ambient temperature and 53±2 % relative humidity.

Polarized light microscopy

The prepared solid dispersion films were investigated by polarized light microscopy (Axiolab, Carl Zeiss, Göttingen, Germany) using a 10x objective. A digital camera (Deltapix, Måløv, Denmark) was

attached to the microscope interfaced with the software Deltapix version 1.6 (Deltapix, Måløv, Denmark). Images were obtained using 120 ms exposure time in TIFF format with a resolution of 1024x1280. Two representative images were obtained at the center of each sample.

Image analysis

Image analysis was performed using in-house written scripts for Matlab (ver. 7.10, Mathworks, USA) making use of the image processing toolbox (ver. 7.10, Mathworks, USA). Since both air bubbles from samples evaporated at high temperatures and nucleated drug gave rise to birefringence, artefacts from air bubbles were removed using in-house written code. Images were gray scaled using a 20% threshold prior to analysis.

Experimental design

A full factorial 2^3 design with three replicates at the center point and one replicate at each corner point was conducted in this study. The investigated factors are: evaporation temperature, PX:PVP ratio and PVP molecular weight.

Table 1 and Table 2 show the low and high levels of each factor and further details on sample abbreviations used in the following discussion. Data were analysed using MODDE (ver. 9.0, Umetrics, Sweden), and the model built was based on partial least squares (PLS) analysis [13]. The monitored responses are the estimates from image analysis: spot count (SC) and percentage area coverage (PAC). Responses are monitored immediately after preparation of the solid dispersion films and after day 30 of storage

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 ^{o}C	50 ^{o}C	70 ^{o}C
PX : PVP	1:1	1:2	1:3
PVP molecular weight	30000 MW	450000 MW	1000000 MW

Table 2: Details of sample name codes. The two digits before C indicate the evaporation temperature.

Sample name code	S1 30C	S1 70C	S2 30C	S2 70C	S3 30C	S3 70C	S4 30C	S4 70C	S5 50C
PX:PVP	1:1	1:1	1:3	1:3	1:1	1:1	1:3	1:3	1:2
PVP grade	K90	K90	K90	K90	K25	K25	K25	K25	K64

3. Results and discussion

Polarized light microscopy

Using SC and PAC as indicators of the extent of nucleation and crystal growth respectively, Figure 1 revealed a clear influence of low and high evaporation temperature on PX stability in the PVP matrix. At a low evaporation temperature, more extensive PX crystallization is observed as compared to a high evaporation temperature. When the evaporation temperature was increased, Figure 1 suggests that the one month stored sample, due to its low PAC, is still in the nucleation phase, while at low evaporation temperature the sample was in the crystal growth phase due to its higher PAC. Another observation from the PLM images is the “stripe–like” crystallization pattern observed at a low evaporation temperature. When the evaporation temperature was increased, the nucleation spots became more randomly distributed.

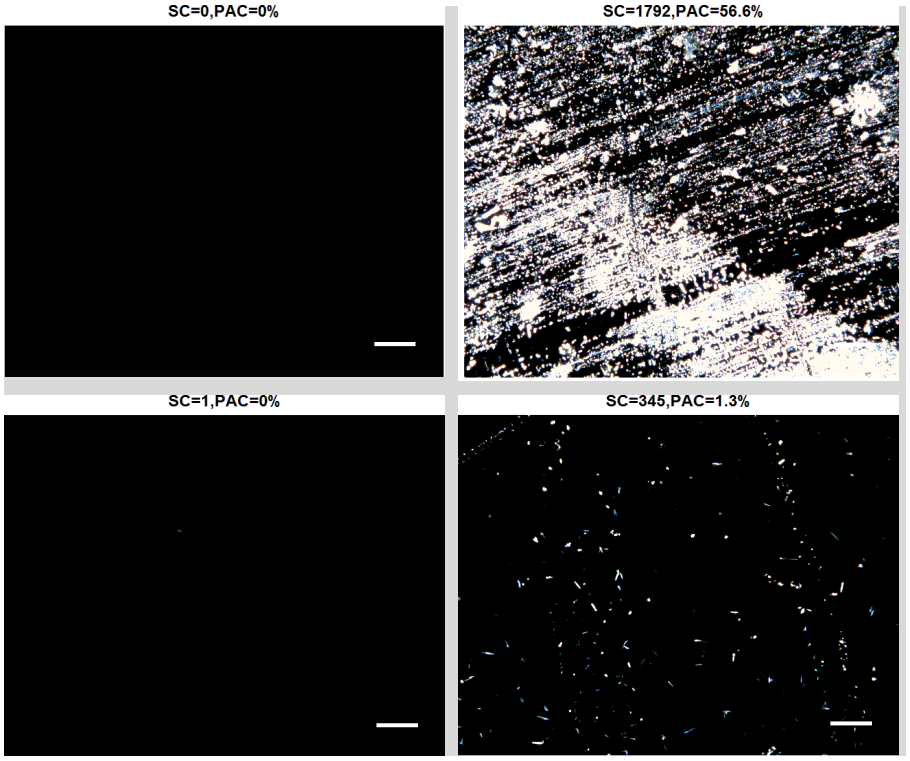

Figure 1: In top images, stability of S3 30C at day 0 (left) and day 30 (right) respectively were observed. In bottom images, stability of S3 70C at day 0 (left) and day 30 (right) respectively were observed. The scale bar is of length 100µm. SC: Spot Count, PAC: Percentage Area Coverage.

Influence of factors

The models developed from the experimental design have in average a goodness of fit of 0.60 and 0.80 for SC and PAC respectively. The effect plot is shown in Figure 2, and indicates that the evaporation temperature accounts for the largest contribution in decreasing the nucleation rate. From the effect plot for PAC shown in Figure 2, the contribution of evaporation temperature accounts as the second largest, while the effect of PX:PVP ratio accounts for the largest amount in decreasing PAC. Thus, the role of increasing evaporation temperature is mainly related to inhibition of nucleation, while its effect on inhibition of crystal growth is secondary. It is likely that an increase in evaporation temperature leads to increased PX stability by two separate causes. Firstly, when the evaporation temperature is increased, there is an increasing likelihood that PX molecules are locked in a random state in the polymer matrix, thus decreasing the extent of nucleation. Secondly, the amount of residual solvents left in the polymer matrix is decreased when evaporation temperature is increased, thus in addition to minimizing plastization the extent of solvent mediated drug crystallization within polymer matrix is minimized.

Increase in the PX:PVP ratio decreases SC in the present study, however due to the large standard deviation, its significance is uncertain. A study from Konno and Taylor has shown that increasing PVP content in solid dispersion decreases the nucleation rate of felodipine in solid dispersion [14]. While increase in polymer molecular weight does not seem to significantly influence SC, its effect is significant in inhibiting the crystal growth. This effect is mainly due to the increased formulation viscosity upon increase in polymer molecular weight.

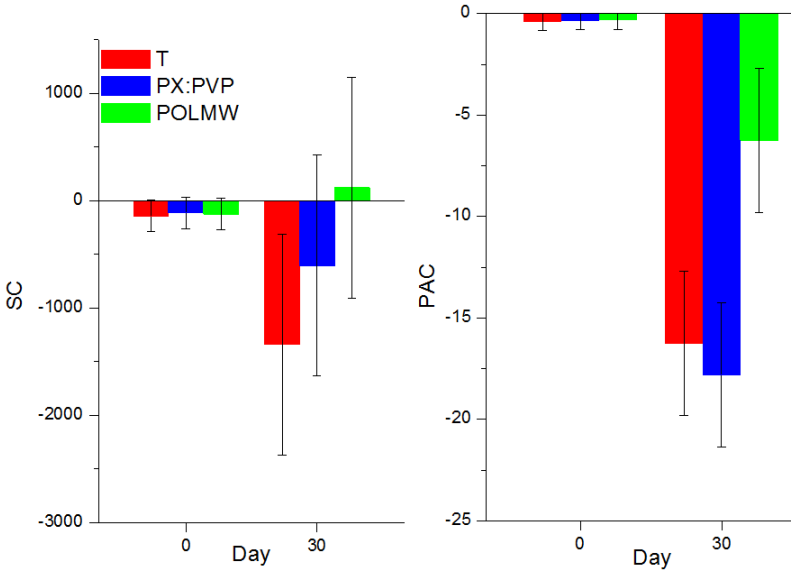

Figure 2: Effect plots from experimental design showing the effects of factors on the investigated responses. T: temperature, PX:PVP: piroxicam:PVP ratio, POLMW: PVP molecular weight.

4. Conclusion

With the use of SC and PAC estimated from image analysis this study highlights future potential of the use of PLM as a tool with quantification ability in high throughput screening of solid dispersions. The experimental design applied highlighted the importance of evaporation temperature on PX stability in the PVP matrix, and showed that in relation to PX stability the effect of temperature is approximately in the same order of magnitude as the PX:PVP ratio.

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