Effect of Polymers on API Precipitation Determined by Polarized Light Microscopy

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ABSTRACT

The purpose of this study was to determine how different polymers effect API precipitation in simulated gastric media by use of polarized light microscopy. Carbamazepine was dissolved in dimethylacetamide and 0.5 µL was placed on a microscope slide. 19.5 µL simulated gastric media was added to the drug solution and a cover glass was placed on top. A camera attached to a polarized light microscope was used to capture a video of the API precipitation.

The developed method is suitable for visualization of API precipitation, and it provides a simple method for evaluating the effect of addition of crystallization inhibitors, like polymers, on the precipitation of API.

INTRODUCTION

For an increasing number of APIs, optimization of the solid form is a central part of the overall strategy to increase the solubility and dissolution rate of the API. This can lead to a supersaturation of API in the stomach and if the supersaturation cannot be maintained the API will precipitate. The solid form composition of the precipitated API and the morphology (size and habit) of the formed crystals can have an influence on the re-dissolution of the API in the intestine and subsequently on drug absorption. Understanding APIs crystallization from a supersaturated solution under simulated gastric conditions is therefore important. Another important aspect of precipitation is to understand how to control the precipitation in a way that can have an effect on the in vivo performance of the API. One possible approach is to add crystallization inhibitors, like polymers, to the formulation.

EXPERIMENTAL METHODS

The model drug carbamazepine was dissolved in dimethylacetamide (DMA) and 0.5 µL was placed on a microscope slide. 19.5 µL simulated gastric media (SGM) (0.1M HCl) was added to the DMA/API solution and a cover glass was placed on top.

A camera (Motic 10MP) attached to a polarized light microscope was used to capture a video of the API precipitation.

To investigate the effect of addition of polymers as crystallization inhibitors 25% (w/w) Kollidon 90F or 10% (w/w) Pharmacoat 615 was dissolved together with carbamazepine in DMA.

The polarized light microscopy images were analyzed using in-house written Matlab routine described in detail by Wu et al.¹. Each image was automatically counted (Count), and percentage area coverage (PAC) calculated according to the following method:

\[
PAC = \frac{A_{sum\ crystalline}}{A_{total\ image}} \times 100 \quad Eq 1
\]

where \(A_{sum\ crystalline}\) and \(A_{total\ image}\) are total crystalline area and image area respectively.

The counting and PAC are taken as responses for nucleation and crystal growth respectively. The number of crystals appearing (Count) as well as percentages of area covered by crystals (PAC) was measured as a function of time. These data was fitted to the following model²:

\[
X = \frac{a}{1 + e^{-\beta (t-t_{50})}} \quad Eq 2
\]

where \(a\) is the maximum Count or PAC, \(\beta\) is the growth constant and \(t_{50}\) is the time where half of the maximum count or PAC was reached.

During the analysis of the different parameter in the equation measurements that were outside the 95% confidence interval were regarded as outliers and removed.

RESULTS AND DISCUSSION

Different concentrations of carbamazepine was used to investigate in what concentration interval the method could be used.

From Figure 1 it can be seen that at low concentrations only a few crystals precipitate in the area captured by the camera causing large variation in the data. At high concentrations the amount of crystals precipitating is too large to analyze using the MatLab routine. It was decided to continue to work with a concentration of 80mg/mL carbamazepine in DMA.

Figure 1: Isolated frames from the captured videos of carbamazepine precipitation from DMA solutions in HCl. The concentration of carbamazepine in the DMA solution was A: 40mg/mL, B: 60mg/mL, C: 80mg/mL and D: 100mg/mL.

Figure 2: Comparison of the parameters from equation 2 after fitting of the equation to the data for number of carbamazepine crystals (Count) detected by image analysis as a function of time for carbamazepine precipitation either without polymer, with Kollidon 90F or with Pharmacoat 615 (n≥6). The asterisk (*) indicates where there is a significant difference (P<0.05) between the parameters for the precipitation of carbamazepine alone and in the present of either Kollidon 90F or Pharmacoat 615.

Figure 2 and 3 show that Kollidon 90F and Pharmacoat 615 have different effects on the precipitation of carbamazepine. Figure 2 shows that Kollidon 90F increases the nucleation rate whereas Pharmacoat 615 seems to decrease it. There is however, no significant difference between the numbers of detected crystals. Figure 3 shows that Pharmacoat 615 decreases the area cover by crystals and that it decreases the crystal growth rate. Kollidon 90F doesn't have a significant effect on the crystal growth of carbamazepine.

CONCLUSION

The developed microscopy based method is suitable for visualization of API precipitation in different simulated gastric media, and provides a fast method for evaluating API precipitation, using only very small amounts of API and media. Using the method it is also possible to evaluate the effect of addition of crystallization inhibitors, like polymers, on the precipitation of API in simulated gastric media. This study showed that Kollidon 90F increases the nucleation rate of carbamazepine whereas no significant effect was seen on the crystal growth. For Pharmacoat 615 it was seen that it has an effect on the nucleation and that it decreases the crystal growth rate.

REFERENCES

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