Mapping the State of a Pharmaceutical Co-precipitation Process: An Integrated Process Analytical Technology (PAT) Approach

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Introduction

In the area of pharmaceutical formulation development, co-precipitation of poorly soluble drugs with polymers is an important technique for improving the dissolution and absorption of drugs. This process has been modified in recent years to prepare extended release preparations. Previous work included optimization of process variables for the preparation of ibuprofen co-precipitates with Eudragit S100 [1], and screening of process and formulation variables for the preparation of extended release Naproxen tablets with Eudragit L 100-55 [2], etc. However, not much work has been reported regarding the use of an integrated Process Analytical Technology (PAT) approach to gain detailed process information and process understanding [3] for a co-precipitation process. On the other hand, crystallization as a critical unit operation for active pharmaceutical ingredient (API) production has attracted a lot of attention [4-5]. Online process analyzers offer excellent opportunities to gain detailed process information for illustrating the progress of a multi-phase process and for elaborating the sequential events that take place during the process. In this work, an integrated PAT approach was developed to map the state of a pharmaceutical co-precipitation process.

Experimental

1. Materials

Naproxen USP (lot No: NPX 368) was obtained from Albemarle Corporation (Orangeburg, SC). Eudragit L 100 (lot No: 1221203048) was obtained from Röhm America Inc. (Somerset, NJ). Solvent A (HPLC grade, lot No: 053546) was provided by Fisher Scientific. Solvent B was obtained from a FDA in-house facility. All of these chemicals and solvents were used without any further processing or purification.

2. Equipment and instruments

Process near infrared (NIR) spectra were acquired with a Luminar™ acoustic-optic tunable-filter (AOTF) based NIR spectrometer (Brimrose Corporation of America,Baltimore, MD), equipped with a transflectance probe. This AOTF NIR spectrometer has the capability of online monitoring the changes in the concentration of the key components in the co-precipitation system. Online turbidity measurement was made possible by a Laboratory Turbidimeter (Model 2100AN, Hach Company, Loveland, Colorado) with a digital fluid pump (Masterflex® L/S® model 7518-10, Cole-Parmer Instrument Company). A flexible tubing connection between the co-precipitation vessel and the sample cell of the turbidimeter was made, such that the fluid could be pumped from the co-precipitation vessel to the sample cell of the turbidimeter for online turbidity measurement, then be returned to

the co-precipitation vessel in the reverse direction. *In situ* real-time monitoring of the particle size evolution (PSE) and particle size distribution (PSD) of the co-precipitation process was accomplished with Mettler-Toledo AutoChem Lasentec FBRM technology (Redmond, WA). Figure 1 is a schematic diagram of the experimental setup and process flow system which includes an on-line PAT monitoring system we designed for the pharmaceutical API/polymer co-precipitation process.

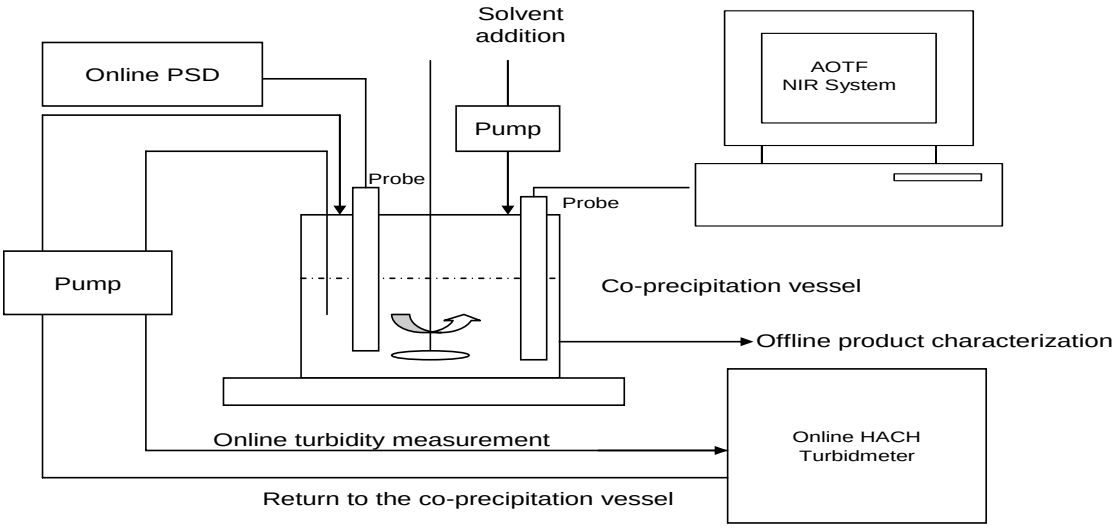

Figure 1. Schematic diagram of experimental setup and process flow system with an on-line PAT monitoring system for pharmaceutical API/polymer co-precipitation process

Results and Discussion

1. Process design

In this work, an integrated online process monitoring approach was developed for a pharmaceutical co-precipitation PAT application. The model drug naproxen was co-precipitated with polymer Eudragit L100 using a binary solvent system. The co-precipitation process was followed in real time by using an on-line acoustic-optic tunable-filter (AOTF) based near infrared (NIR) spectrometer coupled with near real-time measurement of turbidity of the 4-component system. At the same time, the particle size evolution was monitored *in-situ* by using Lasentec FBRM technology during the course of co-precipitation induction, nucleation, and growth. By examining the NIR spectra and turbidity curve together, the sequential process events of incubation, nucleation, and growth were determined so the state of the process could be visualized in three-dimensional space.

2. Product characterization

The final co-precipitated product was characterized by using off-line NIR spectroscopy. The composition of the final co-precipitated product was quantified by employing a pre-established multivariate calibration model constructed for this work.

3. Three-dimensional map of process state

By integrating information and knowledge gained from this study, a three-dimensional map of the co-precipitation process was constructed showing process time-wave number-NIR absorption intensity. On this map, various process signatures, including time sequential events during the process evidenced by both thermodynamic and kinetic information, have been identified and explained.

Conclusion

This work provides a concrete case study that focuses on a process for pharmaceutical PAT application. To the best of our knowledge, it is the first report of using an integrated PAT approach to understand a pharmaceutical co-precipitation process, and to visualize this technologically important process in a 3-dimensional map. This information and knowledge are valuable in terms of determining a suitable design space and operational process space for a pharmaceutical unit operation.

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Disclaimer

The views and opinions expressed in this paper are only those of the authors, and do not necessarily reflect the views or policies of the FDA.

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