Continuous crystallization of carbamazepine: Set-up and monitoring using process analytical technology tools

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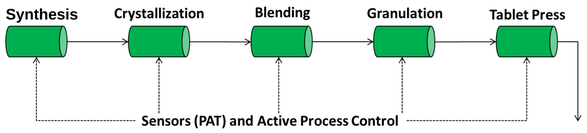
Abstract

FDA is taking proactive steps to facilitate innovation and modernization of pharmaceutical development and manufacturing to improve manufacturing efficiency, robustness, and assurance of drug quality. CDER's emerging technology program supports the adoption of innovative technologies through early engagement with sponsors. One such emerging technology is continuous manufacturing (CM). One of the challenges for implementing CM for API production is the development of the continuous crystallization step. Crystallization can have significant impact on the physiochemical properties of drug substance such as particle size, shape, purity and polymorphism. Research efforts on continuous crystallization have increased significantly in the past few years. This presentation discuss a case study on the risk factors involved in the development of a continuous crystallization process for a model compound, carbamazepine (CBZ). A lab-scale, automated two-stage mixed suspension mixed product removal (MSMPR) platform for CBZ was engineered and set up to monitor the crystallization process. The system was integrated with online process analytical technology (PAT) tools such as Raman spectroscopy (to monitor the polymorph and CBZ concentration) and focused beam reflectance microscopy (FBRM, to monitor particle size). The MSMPR system was also designed with feedback/feedforward controls to achieve constant levels in crystallizers, a centralized automation program coded in LabVIEW. The performance and control of the continuous crystallization process was demonstrated and methods to detect changes in process quality were validated. The research has generated in-house data and knowledge for the Agency which has informed CDER's Emerging Technology Team feedback and recommendations to sponsors and supported the development of ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products Guidance.

Introduction

End to End Continuous Manufacturing



Continuous manufacturing is the continuous feeding of input materials into, the transformation of in-process materials within, and the removal of output materials from the process. End to End CM is the manufacturing of the drug product from starting materials in a single integrated process.

Benefits of CM:

- **Integrated processing with fewer steps and shorter processing times**
- **Small equipment and facilities reducing costs**
- **Online monitoring and control for increased product quality assurance in real time**
- **Eliminating bottlenecks related to scale-up enabling more flexible responses to public health emergencies**
- **Enabling new synthetic pathways and greener chemistry**
- **Enabling faster product development**

Introduction

While there have been several approvals of drug products manufactured using continuous manufacturing, there have been no approved products using end-to-end continuous manufacturing (E2E CM). Several sponsors have engaged CDER's Emerging Technology Team requesting feedback on the development of E2E CM. There also have several recent US-government contracts awarded to establish US based continuous drug substance and E2E CM manufacturing facilities. One of the key steps in enabling continuous drug substance and E2E CM is continuous crystallization.

Continuous Crystallization

Crystallization is key purification step in drug substance manufacturing

Batch Crystallization	Continuous Crystallization
• Well understood • Easier to design • Simple scale-up	• Superior controllability • Less downtime • Smaller footprint • Aligned with quality-by-design (QbD) paradigm • Lower inventory on hand • Enhanced polymorph control

-What are possible process failures and how to avoid these issues?
-How and which PAT tools should be used for monitoring the process dynamics

Process failures in Continuous Crystallization process

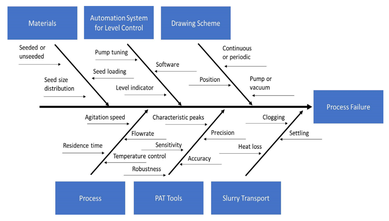


Figure 1. Ishikawa diagram that shows possible causes for failure in a continuous crystallization process

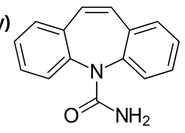
Regulatory Developments

FDA's goal: Develop a framework for regulation of Continuous Manufacturing (CM) Systems and support development of ICH Q13

Materials and Methods

- **Mettler Toledo Easy Max 402 system**
- **2-stage (Mixed Suspension Mixed Product Removal (MSMPR)**

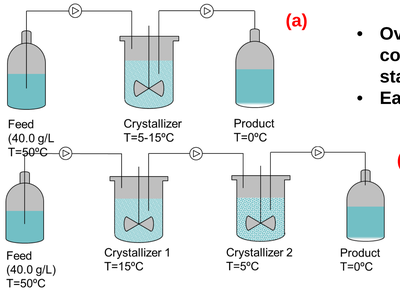
- **Carbamazepine (CBZ) (model compound)**
- **Anticonvulsant- treat seizers and nerve pain**
- **BCS Class II (low solubility and high permeability)**
- **Widely studied in batch crystallization**
- **Four isolated and characterized polymorphs**
  - **Form I: Triclinic**
  - **Form II: Trigonal**
  - **Forms III & IV: Monoclinic**



Target form III

Results and Discussion

2-Stage Crystallization



- **Overall yield 45% compared to 7% with 1-stage crystallization**
- **Easy transfer of crystals**

Figure 2. (a) One-stage crystallization process, and (b) 2-Stage crystallization process

Automation Control

- **Pump flow control-Manual or computer control using LABVIEW**
- **Level Indication and Control-Pneumatic set-up integrated with LABVIEW**

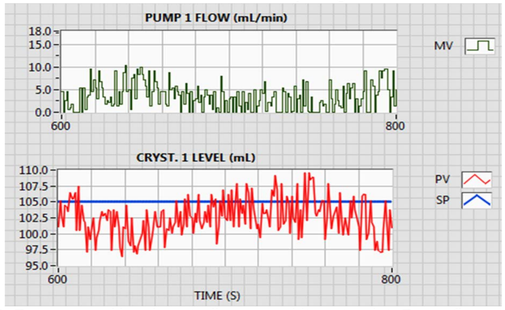


Figure 3. Response of level controller around its set point. Pump flow rate is at the top figure and the level measurement and set point of 105 mL are shown at the bottom figure.

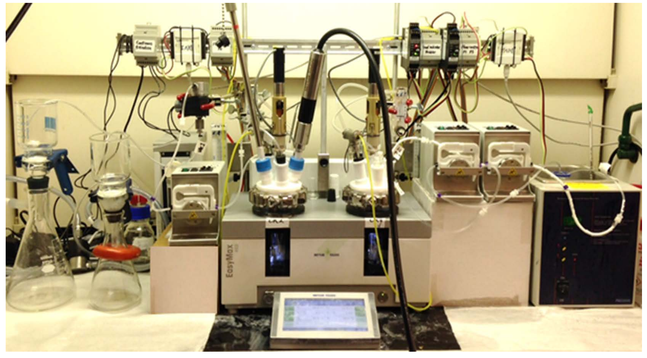


Figure 4. Two-stage MSMPR system with implemented PAT tools and periodic filtration unit.

Process Analytical Technology (PAT) Tools

Maintain and Monitor State of Control-Integrate PAT tools

1) Focused Beam Reflectance Measurement (FBRM): Chord length distributions (CLD); monitor steady state and any disturbances (Mettler Toledo system)

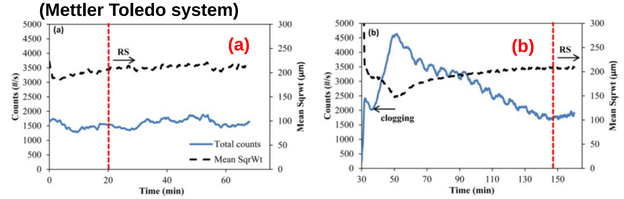


Figure 5. FBRM data representing steady state operation for case studies for (a) no clogging event and (b) one clogging event

2) Raman Spectroscopy: Measure CBZ concentration and distinguish Form II and Form III (Kaiser Raman system)

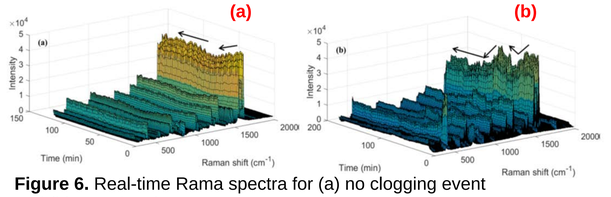


Figure 6. Real-time Rama spectra for (a) no clogging event and (b) one clogging event

- **Raman method was validated for accuracy, precision, LOQ, LOD and robustness and compared with HPLC analysis**

Theoretical Conan (mg/mL)	Predicted Conan ± stdev (mg/mL)					
	Model 1	Model 2	Model 3	Model 4	Model 5	HPLC
1S	16.2 ± 0.06	16.1 ± 0.05	15.7 ± 0.05	16.2 ± 0.04	14.4 ± 0.04	15.3 ± 0.18
2S	23.0 ± 0.66	23.0 ± 0.54	23.0 ± 0.58	22.7 ± 0.55	22.8 ± 0.66	25.1 ± 0.63
3S	31.7 ± 0.87	30.7 ± 0.79	31.1 ± 0.83	30.4 ± 0.82	30.5 ± 0.82	34.4 ± 2.45
4S	43.9 ± 1.21	42.3 ± 1.24	43.3 ± 1.23	41.4 ± 1.23	41.4 ± 1.21	44.9 ± 1.24
5S	52.7 ± 1.08	51.6 ± 1.19	52.8 ± 1.16	50.7 ± 1.23	50.7 ± 1.22	52.7 ± 1.96
6S	61.3 ± 1.07	61.2 ± 1.27	62.6 ± 1.21	60.7 ± 1.36	60.7 ± 1.34	62.5 ± 3.66

Conclusions

- **A proof-of-concept 2-stage cooling MSMPR system was set up with automated controls and semi-continuous filtration system.**
- **Level control system with bottom-draw suspension removal and alternating filtration system was developed.**
- **PAT tools (FBRM and Raman) were integrated to monitor the process in real time.**
- **Issues of clogging was addressed and was detected by the PAT methods.**
- **Raman PAT method for monitoring solute concentration and state of control was developed and validated.**

References

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