

**QUALITY-BY-DESIGN (QbD) BASED  
CRYSTALLIZATION PROCESS DEVELOPMENT  
FOR PHARMACEUTICAL API**

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**June 2023**

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FOR PHARMACEUTICAL API**

by

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Submitted

in fulfilment of the requirements of the degree of **Doctor of Philosophy**

to the



**Indian Institute of Technology Delhi**

**June 2023**

## **Certificate**

This is to certify that the thesis entitled “**QUALITY-BY-DESIGN (QbD) BASED CRYSTALLIZATION PROCESS DEVELOPMENT FOR PHARMACEUTICAL API**” being submitted by **MANU GARG** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** is a record of the original bonafide research work carried out by him under my guidance and supervision. The results contained in this thesis have not been submitted in part or in full to any other University or Institute for the award of any degree or diploma.

I certify that he has pursued the prescribed course of research.

**Prof. Anurag S. Rathore**

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## **Acknowledgements**

This thesis would not have been materialized without the immeasurable help from many people who gave their support in different ways. To them I would like to convey my heartfelt gratitude and sincere appreciation.

I owe my deepest gratitude to my Professor, Dr. Anurag S. Rathore for his encouragement and support in each phase of my research endeavor. As a supervisor, he has mentored my research work from the beginning of the doctoral program. Personally, as a well-wisher he helped me to overcome numerous obstacles. He supported me not only as a research guide but, also emotionally, giving ample moral support and freedom.

With his insightful discussions and constructive feedback, he channelized my research work in proper direction. Being my inspiration, he taught me how to execute research projects in a perfect manner. Without his guidance and continuous optimism this thesis would not have been possible. I owe my profound thanks to him for his constant support and his effort to shape my dissertation till the last moment. He is an unrivalled mentor who accompanied throughout the gestation of my work. I am very grateful for his trust in me and his positive stimulation.

I am pleased to acknowledge my PhD research committee members, Prof. Sudip Pattanayek, Prof. Sreedevi Upadhyayula and Prof. Arunachalam Ramanan for their significant influence in formulating the ideas. Their insights helped me move forward.

I specially thank Prof. Paresh Chokshi for the guidance provided for mechanistic modeling of crystallization processes.

I would like to specially thank the R&D leadership team of Sun Pharmaceutical Industries Ltd – Dr. Mohan Prasad, Mr. Raghvendra Prasad and Mr. Bhupendra Vashishta for their kind support and co-operation during this work.

No words of gratitude can justify the support, help and care I have received from my dear friends Dr. Nikhil Kateja, Dr. Shalini Shikha, Dr. Ananth Govind Rajan and Dr. Ramkinkar Santra.

I would also like to gratefully acknowledge the support of all the bachelor's degree students- Mr. Milan Roy, Mr. Akshat Lohiya and Ms. Perna Kumari for their help rendered in carrying out experiments.

Special thanks to my parents Dr. Atul Garg and Dr. Shikha Agrawal, and my wife Mrs. Shruti Tyagi, who have put in their efforts and prayers for me to attain success in life. I am falling short of words to express my feelings towards them. Their blessings, belief and encouragement were essential for successful completion of this work.

**MANU GARG**

## Abstract

While the concept of Quality-by-Design (QbD) has been explored for more than a decade, its implementation in crystallization of active pharmaceutical ingredient (API) is limited and a subject of ongoing development. Researchers have explored various novel technologies in recent years to get product of desired quality directly from crystallization. However, there are limited instances of successful implementation of this approach for the process of pharmaceutical crystallization. Till date, there is limited understanding and major concerns regarding implementation of QbD and process analytical technology (PAT) in the pharmaceutical arena. The objective of this work is therefore to provide a comprehensive understanding on various aspects of QbD and PAT, along with addressing the concerns related to their implementation to achieve automation of the pharmaceutical process. In this thesis, we attempt to alleviate a number of challenges associated with pharmaceutical drug quality by following a QbD based approach: (a) development of a mechanistic model of anti-solvent aided crystallization process; (b) implementing Design-of-Experiments (DoE) for anti-solvent aided crystallization process; (c) implementing model-based control for particle size distribution in anti-solvent aided crystallization process using PAT; and (d) evaluating impact of crystallization process parameters on particle morphology and dissolution behaviour of drug substance.

Thorough process understanding is a prerequisite for implementing QbD in development of a pharmaceutical crystallization process. Identification of the critical process parameters (CPP) and raw material attributes and creation of mechanistic models that can correlate these to the product quality attributes are the first steps in this approach. In Chapter 3, a comprehensive model for antisolvent crystallization has been developed by solving population balance equation (PBE) along with considering dependence of crystal growth rate on crystal size and kinetic parameters for nucleation and growth rates. The proposed model compares favourably to other similar models in the literature with respect to the accuracy of prediction of crystal size, surface area, and volume, even at varying feed rate profiles of antisolvent during crystallization. The average residual value obtained in the given model is of the order of  $1/10^{\text{th}}$  of the previously published models. The superlative performance likely originates from the fact that most models ignore the size dependence of crystal growth rate. It is expected that the proposed model to be a useful tool in the arsenal of those involved in development of pharmaceutical crystallization.

Chapter 4 focuses on implementation of a DoE driven QbD approach for the anti-solvent crystallization of dexlansoprazole API with the help of focused beam reflectance measurement (FBRM) PAT. An empirical model has been created using Minitab19 software to design a control strategy for managing crystal size distribution during crystallization. In this work, screening study was performed on 7 crystallization parameters to identify CPP with respect to particle size. The shortlisted critical process parameters (reactor temperature and addition time of anti-solvent) were then subjected to full factorial study for deriving an empirical model having a resultant R-square value of more than 80%. The derived model was also found to support the theoretical growth rate equation. This work demonstrates how DoE-based experimentation can be used to implement QbD for a pharmaceutical anti-solvent crystallization process.

In Chapter 5, we demonstrate the use of derived empirical model for controlling the particle size during crystallization, when the system is exposed to planned disruptions under the PAT framework. The effect on particle size distribution was measured in terms of chord length distribution with the help of FBRM PAT. In this study, during crystallization of dexlansoprazole, the dosing pump feeding anti-solvent (n-heptane) was shut down temporarily and the remaining anti-solvent quantity was added under different process conditions derived from the empirical model targeting a desired set-point value of FBRM percentile C50 value. The C50 value in model-based experiments (23.2  $\mu$ , 24.2  $\mu$ ) were observed to be in close range with the baseline experiment (23.1  $\mu$ ) while the experiment with model-free approach showed significant deviation (32.9  $\mu$ ). The motivation was to check the effectiveness of model to design a PAT based control scheme that can deliver particle sizes close to the desired values after making suitable real-time changes to the CPPs.

In Chapter 6, the impact of crystallization process parameters on solid-state behaviour of dexlansoprazole has been elucidated by utilizing various characterization techniques and derive a model for intrinsic dissolution rate using JMP14 software for development of appropriate pharmaceutical dosage forms. The dexlansoprazole samples prepared under different crystallization conditions of temperature and anti-solvent addition rate were subjected to characterization performed using a variety of analytical techniques, including particle size distribution (PSD) by laser diffraction, X-ray powder diffraction (XRPD), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapour sorption (DVS), and intrinsic dissolution rate (IDR). Intrinsic dissolution rate of API was found to be enhanced by keeping lower reactor temperature and faster addition of anti-solvent during crystallization. This observation was supported and well

explained with the help of characterization data generated with the above mentioned analytical techniques.

We believe that the studies presented here as a part of this thesis will promote development of robust and automated crystallization platforms for manufacturing of pharmaceuticals.

## सार

जबकि गुणवत्ता-दर-डिजाइन (क्यूबीडी) की अवधारणा को एक दशक से अधिक समय से खोजा गया है, सक्रिय फार्मास्युटिकल सामग्री (एपीआई) के क्रिस्टलीकरण में इसका कार्यान्वयन सीमित है और चल रहे विकास के अधीन है। शोधकर्ताओं ने क्रिस्टलीकरण से सीधे वांछित गुणवत्ता के उत्पाद प्राप्त करने के लिए हाल के वर्षों में विभिन्न नवीन तकनीकों की खोज की है। हालांकि, फार्मास्युटिकल क्रिस्टलाइजेशन की प्रक्रिया के लिए इस दृष्टिकोण के सफल कार्यान्वयन के सीमित उदाहरण हैं। आज तक, फार्मास्युटिकल क्षेत्र में क्यूबीडी सिद्धांतों और विश्लेषणात्मक प्रौद्योगिकी (पीएटी) के कार्यान्वयन के संबंध में सीमित समझ और प्रमुख चिंताएँ हैं। इसलिए इस कार्य का उद्देश्य फार्मास्युटिकल प्रक्रिया में स्वचालन प्राप्त करने के लिए इसके कार्यान्वयन से संबंधित चिंताओं को दूर करने के साथ-साथ क्यूबीडी और पीएटी के विभिन्न पहलुओं पर एक व्यापक समझ प्रदान करना है। इस थीसिस में, हम क्यूबीडी दृष्टिकोण का पालन करके फार्मास्युटिकल दवा की गुणवत्ता से जुड़ी कई चुनौतियों को दूर करने का प्रयास करते हैं: (अ) एंटी-सॉल्वेंट एडेड क्रिस्टलीकरण प्रक्रिया के यंत्रवत मॉडल का विकास; (ब) एंटी-सॉल्वेंट एडेड क्रिस्टलाइजेशन प्रक्रिया के लिए डिजाइन-ऑफ-एक्सपेरिमेंट (डीओई) को लागू करना; (स) पीएटी का उपयोग करके एंटी-सॉल्वेंट एडेड क्रिस्टलाइजेशन प्रक्रिया में कण आकार वितरण के लिए मॉडल-आधारित नियंत्रण लागू करना; (द) दवा पदार्थ के कण आकारिकी और विघटन व्यवहार पर क्रिस्टलीकरण प्रक्रिया मापदंडों के प्रभाव का मूल्यांकन करना।

पूरी तरह से प्रक्रिया समझ एक दवा क्रिस्टलीकरण प्रक्रिया के विकास के दौरान डिजाइन द्वारा गुणवत्ता को लागू करने के लिए एक शर्त है। महत्वपूर्ण प्रक्रिया मापदंडों और कच्चे माल की विशेषताओं की पहचान और मशीनी मॉडल का निर्माण जो इन्हें उत्पाद की गुणवत्ता विशेषताओं से संबंधित कर सकते हैं, इस दृष्टिकोण में पहला कदम है। अध्याय तीन में, क्रिस्टल आकार पर क्रिस्टल विकास दर की निर्भरता पर विचार करने के साथ-साथ न्यूक्लियेशन और विकास दर के लिए गतिज मापदंडों पर विचार करने के साथ-साथ जनसंख्या संतुलन समीकरण (पीबीई)

को हल करके एंटीसॉल्वेंट क्रिस्टलीकरण के लिए व्यापक मॉडल विकसित किया गया है। प्रस्तावित मॉडल क्रिस्टलीकरण के दौरान एंटीसॉल्वेंट के अलग-अलग फीडेट प्रोफाइल पर भी क्रिस्टल आकार, सतह क्षेत्र और मात्रा की भविष्यवाणी की सटीकता के संबंध में अन्य समान मॉडल के अनुकूल तुलना करता है। दिए गए मॉडल में प्राप्त औसत अवशिष्ट मूल्य पिछले मॉडल के 1/10 के क्रम का है। अतिशयोक्तिपूर्ण प्रदर्शन की संभावना इस तथ्य से उत्पन्न होती है कि अधिकांश मॉडल क्रिस्टल विकास दर के आकार की निर्भरता को अनदेखा करते हैं। यह उम्मीद की जाती है कि प्रस्तावित मॉडल फार्मास्युटिकल क्रिस्टलाइजेशन के विकास में शामिल लोगों के शस्त्रागार में एक उपयोगी उपकरण होगा।

अध्याय चार फोकस्ड बीम रिफ्लेक्टेंस मेजरमेंट पीएटी की मदद से डेक्सलानोसोप्राजोल एपीआई के एंटी-सॉल्वेंट क्रिस्टलाइजेशन के लिए डीओई संचालित क्यूबीडी दृष्टिकोण के कार्यान्वयन पर केंद्रित है। क्रिस्टलीकरण के दौरान क्रिस्टल आकार वितरण के प्रबंधन के लिए नियंत्रण रणनीति तैयार करने के लिए मिनीटैब19 सॉफ्टवेयर का उपयोग करके एक अनुभवजन्य मॉडल बनाया गया है। इस कार्य में, कण आकार के संबंध में सीपीपी की पहचान करने के लिए 7 क्रिस्टलीकरण मापदंडों पर स्क्रीनिंग अध्ययन किया गया था। शॉर्टलिस्ट किए गए महत्वपूर्ण प्रक्रिया मापदंडों (रिएक्टर तापमान और एंटी-सॉल्वेंट के अतिरिक्त समय) को 80% से अधिक के परिणामी आर-स्कवायर मान वाले अनुभवजन्य मॉडल को प्राप्त करने के लिए पूर्ण तथ्यात्मक अध्ययन के अधीन किया गया था। व्युत्पन्न मॉडल को सैद्धांतिक विकास दर समीकरण का समर्थन करने के लिए भी पाया गया। यह कार्य प्रदर्शित करता है कि कैसे डीओई आधारित प्रयोग का उपयोग क्यूबीडी को एक फार्मास्युटिकल एंटी-सॉल्वेंट क्रिस्टलीकरण प्रक्रिया के लिए लागू करने के लिए किया जा सकता है।

अध्याय पाँच में हम क्रिस्टलीकरण के दौरान कण आकार को नियंत्रित करने के लिए व्युत्पन्न अनुभवजन्य मॉडल के उपयोग को प्रदर्शित करते हैं, जब सिस्टम को पीएटी ढांचे के तहत नियोजित व्यवधानों के संपर्क में लाया जाता है। कण आकार वितरण पर प्रभाव को एफबीआरएम

पीएटी की मदद से कॉर्ड लंबाई वितरण के संदर्भ में मापा गया था। इस अध्ययन में, डेक्सलांसोप्राज़ोल के क्रिस्टलीकरण के दौरान, डोज़िंग पंप फीडिंग एंटी-सॉल्वेंट (एन-हेप्टेन) को अस्थायी रूप से बंद कर दिया गया था और वांछित सेट-पॉइंट पर्सेंटाइल सी50 वैल्यू को लक्षित करने वाले अनुभवजन्य मॉडल से प्राप्त विभिन्न प्रक्रिया स्थितियों के तहत शेष एंटी-सॉल्वेंट मात्रा को जोड़ा गया था। मॉडल-आधारित प्रयोगों में C50 मान ( $23.2 \mu$ ,  $24.2 \mu$ ) को बेसलाइन प्रयोग ( $23.1 \mu$ ) के निकट सीमा में देखा गया, जबकि मॉडल-मुक्त दृष्टिकोण वाले प्रयोग में महत्वपूर्ण विचलन ( $32.9 \mu$ ) दिखाया गया। प्रेरणा पीएटी आधारित नियंत्रण योजना को डिजाइन करने के लिए मॉडल की प्रभावशीलता की जांच करना था जो सीपीपी में उपयुक्त वास्तविक समय परिवर्तन करने के बाद वांछित मूल्यों के करीब कण आकार प्रदान कर सके। अध्याय छह में, डेक्सलांसोप्राज़ोल के ठोस-अवस्था व्यवहार पर क्रिस्टलीकरण प्रक्रिया मापदंडों के प्रभाव को विभिन्न लक्षण वर्णन तकनीकों का उपयोग करके स्पष्ट किया गया है और उचित दवा खुराक रूपों के विकास के लिए जेएमपी 14 सॉफ्टवेयर का उपयोग करके आंतरिक विघटन दर के लिए एक मॉडल प्राप्त किया गया है। तापमान और एंटी-सॉल्वेंट जोड़ दर की विभिन्न क्रिस्टलीकरण स्थितियों के तहत तैयार किए गए डेक्सलांसोप्राज़ोल के नमूनों को लेजर विवर्तन, एक्स-रे पाउडर विवर्तन (एक्सआरपीडी), स्कैनिंग इलेक्ट्रॉन द्वारा कण आकार वितरण (पीएसडी) सहित विभिन्न विश्लेषणात्मक तकनीकों का उपयोग करके प्रदर्शन के अधीन किया गया था। माइक्रोस्कोपी (एसईएम), डिफरेंशियल स्कैनिंग कैलोरीमेट्री (डीएससी), थर्मोग्रैविमेट्रिक एनालिसिस (टीजीए), डायनेमिक वेपर सोरशन (डीवीएस), और आंतरिक विघटन दर (आईडीआर)। रिएक्टर का तापमान कम रखने और क्रिस्टलीकरण के दौरान एंटी-सॉल्वेंट को तेजी से जोड़ने से एपीआई की आंतरिक विघटन दर में वृद्धि पाई गई। उपर्युक्त विश्लेषणात्मक तकनीकों से उत्पन्न लक्षण वर्णन डेटा की सहायता से इस अवलोकन का समर्थन किया गया और अच्छी तरह से समझाया गया।

हमारा मानना है कि इस थीसिस के एक हिस्से के रूप में यहां प्रस्तुत किए गए अध्ययन फार्मास्यूटिकल्स के निर्माण के लिए मजबूत और स्वचालित क्रिस्टलाइजेशन प्लेटफॉर्म के विकास को बढ़ावा देंगे।

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