USE OF PAT FOR ACTIVE PHARMACEUTICAL INGREDIENT CRYSTALLIZATION PROCESS CONTROL

Huiquan Wu and Ajaz S. Hussain[1]

Office of Pharmaceutical Science (OPS), HFD-003
Center of Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
5515 Security Lane, Room 7234, Rockville, MD 20852, USA
[1]Corresponding author: hussaina@cder.fda.gov; 1-301-594-2847 (Phone)

Abstract: Crystallization of active pharmaceutical ingredient (API) or pharmaceutical drug substances is a crucial unit operation. In this paper challenges and scientific progress over the last two decades in the areas of pharmaceutical crystallization thermodynamics, kinetics, polymorphism, process modeling, and process control were attempted. Effective utilization of such scientific knowledge for optimized control of API crystallization process was discussed. A conceptual PAT framework for API crystallization process control was proposed. Three case studies from the literatures were discussed as hypothetical examples to illustrate the application of PAT framework to pharmaceutical crystallization process.

Keywords: process control, process models, product quality, knowledge-based control, systems concepts, on-line control

1. INTRODUCTION

Both the design of crystallization vehicle and the crystallization process control have significant impact on the crystal quality attributes of active pharmaceutical ingredients (APIs) and drug substances, such as crystal size distribution (CSD), mean crystal size, morphology, and purity. However, due to its complexity of the multivariate nature of pharmaceutical crystallization process, product and process design of the pharmaceutical crystals have been empirically to large extent, advanced process control strategies available from other industrial sectors have not been intensively implemented either. A knowledge-based and systems approach to the pharmaceutical crystallization is much desirable from both process control and regulatory perspective. In this paper, an overview of scientific progress over the last two decades in the area of crystallization was attempted. A strategy of how this knowledge being utilized in a regulatory setting under the FDA's Process Analytical Technology (PAT) Initiative was proposed. Three hypothetical examples were used to illustrate the key components of the PAT framework as applied to API crystallization process control.

2. BODY OF KNOWLEDGE IN CRYSTALLIZATION CONTROL

There are many aspects for pharmaceutical crystallization process control, such as (a) CSD, (b) crystal habit and purity, (c) polymorphism, (d) salting (fouling), (e) capacity and scale-up, and (f) crystallizer stability. Numerous researches have enriched and advanced its fundamental understanding.

2.1 Crystallization thermodynamics

Chemical engineering thermodynamics can help to identify operational zone for process design and enhance process efficiency, and to provide information about process limits. Metastable thermodynamic states are frequently encountered in many occasions such as: (a) pharmaceutical systems, (b) intentional or unintentional creation of supersaturation, (c) crystallization of desired solid-state modifications, and (d) control of solid-state conversion during isolation, manufacturing storage, and dissolution. However, due to the proprietary nature of pharmaceutical development, very few pharmaceutical R&D organizations have published their results on pharmaceutical crystallization thermodynamics (Starbuck, *et al*., 2002). Metastable zone width and nucleation (Ulrich and Strege, 2002), dissolution and phase transition of pharmaceutical compounds (Garcia, *et al*., 2002), solution-mediated phase transformation (Murphy, *et al*, 2002) have been reported. A mini review (Hornedo and Murphy, 1999) summarized works on supersaturation and nucleation prior to 1998.

2.2 Crystallization kinetics and design of crystallizers

Crystallization is a multi-steps process in terms of mass transport. In the case of kinetic control, the CSD and types of crystals will be determined to a large extent by the crystallization kinetics. Over the years, many powerful techniques for quantitative phase analysis, such as X-ray powder diffraction, Vibrational spectroscopy, NMR spectroscopy have been used for pharmaceutical crystallization kinetics study (Stephenson, *et al*., 2001). For the antiviral drug UC-781, Damian *et al*. (2001) found out that both kinetic parameters of crystallization (*k*), and characteristic temperature parameters can be applied to assess the stability of pharmaceutical compounds which are prone to crystallization. Alamdari and Tabkhi (2004) fitted the mechanistic model to the kinetic data from an industrial MSMPR (Mixed-Suspension Mixed-Product Removal) crystallizer, which generated the growth and nucleation rate equations for hexamine crystallization in industrial scale. The prediction of CSD using the MSMPR model is based on two assumptions: well-mixing and hydrodynamic effects ignorable. Such assumptions greatly limit the use of the model: the design being extremely conservative, not optimized for yield or operation. The problems are even worse at the current regulatory setting, because the new drug applications (NDAs) are filed and approved based on the data from 3 validation batches. Once approved, space is limited for changing operation profile and modifying the design. The lack of fundamental understanding of the flow dynamics in the crystallization vehicles and crystallizing kinetics often becomes the bottlenecks for process development, scale up or scale down, and process optimization. In this regard, computational fluid dynamics (CFD) coupling with population balance equation (PBE) could be used to address changes in particle population in wide range of applications, thus holds promising to crystallizer design.

2.3 Polymorphism and its characterization

Pharmaceutical crystalline solids can exist in the form of polymorphs, solvates or hydrates. Unanticipated polymorphic changes of a drug substance can affect chemical and physical stability, solubility, morphology, hygroscopicity, and, ultimately, bioavailability. Therefore, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development. Yu, *et al*. (1998) reviewed progress on key elements of polymorph characterization (identification and quantification, structures, properties and structure-property relationships). New application of characterization techniques such as terahertz pulse spectroscopy for identification pharmaceutical polymorphs was reported for polymorphs of ranitidine hydrochloride (Taday, et al., 2003). Identification of polymorphism and know when/how it occurs are proven to be challenging for pharmaceutical formulation scientists and process engineers. For polymorphism of stavudine (forms I, II, and III), Gandhi, *et al*. (2000) studied the stability and potential for inter-conversation of the forms. This information will help the selection of preferred form for development and commercialization.

2.4 Process modeling

Crystallization process modeling has been a very challenging topic, due to two reasons: (1) the complicity of the crystallization process itself; (2) much of the knowledge about many pharmaceutical significant crystallization systems being limited to phenomenological and empirical level, an integrative approach to the crystallization system being largely lacked. The significant progress in the area of industrial crystallization and crystal growth facilitates the process modeling effort.

Multivariate Statistics Modeling (MVSM). This has been widely used to establish the correlation between the input and output variables of a process, or correlation between the independent and response variables of a design of experiment (DOE). However, the quality of MVSM highly depends on both the quality of the data collected and the design space covered. The MVSM should be built on a well designed experiment, which requires that three core elements (representative-ness, randomness, and replication) should be well reflected and balanced in DOE, such that the design space is able to accommodate variability that may occur during the application of the model. Togkalidou, *et al*. (2001)

used a fractional factorial experiment design to investigate relative effects of operating conditions on the filtration resistance of a slurry produced in pharmaceutical semi-continuous batch crystallizer. An empirical model constructed between the operating variables and filtration resistance was used to define the factory operating procedure, which reduced filtration time 3.7 fold. Using fiber-optic NIR spectroscopy, Fevotte, *et al*. (2004) established a multivariate calibration model to provide measurements of the polymorphic composition of the solid product (SaC, an API) which is likely to appear in two crystalline forms or in the amorphous state. A recent review (Miletic, *et al*., 2004) highlighted features that are important in the successful development of on-line MVSM applications.

Population balance modeling Population balance equations (PBE) are capable of describing the temporal evolution of particle property distributions, in particular of particle size distributions. Applying PBE to industrial crystallization was set forth in 1960s by two pioneers Randolph and Larson (1988), and has gain popularity and success (Wynm and Hounslow, 1997; Puel, *et al*., 2003; Georgieeva, *et al*., 2003; Meadhra and Rosmalen, 1996; Monnier, *et al*., 1997). The main challenges and progress in the area of PBE can be summarized briefly below. (1) For most batch crystallization processes, it remains difficult to obtain relevant on-line information on both the dissolved solid concentration in the liquid phase and CSD. Moreover, the reported experimental results are generally based upon simplified population balance models such as moment equations which are known to contain insufficient information on the CSD (Monnier, *et al*., 1997). Advancement in on-line instrumentation, on-line process sensors, and computation technologies over the last decade greatly enhances our capability to overcome the challenges.
(2) The process dynamics and its time characteristics of crystallization system can be modeled by solving a number of system mass and energy balance, as well as a PBE (Meadhra, 1996), coupled with residence-time-distribution (Wynm, 1997). The complexity and nonlinearity of the equations presents additional challenges. Advancements in computation methodologies and algorithms (Puel, *et al*., 2003) are very helpful. (3) There are great difficulties in expressing accurately nucleation and crystal growth rates and especially the complex phenomena of agglomeration in the relevant population balance. The overlap between nucleation and crystal growth adds additional difficulty. Approach proposed by S. Feyo de Azevedo's group such as knowledge based modular (KBM) networks (Peres, *et al*.,2001) and knowledge-based hybrid (KBH) modeling approach (Georgieeva, *et al*., 2003) appears to be promising to overcome these barriers.

First principle modeling For first principle modeling, understanding of the process mechanism for the overall process is needed. While conducting the particle design of ketoprofen using spherical crystallization process by batch quasi-emulsion method, Espitalier *et al*. (1997a, b) found that ketoprofen presents a large metastable zone in the case of primary nucleation and a very narrow metastable zone in the case of secondary nucleation. To produce spherical agglomerates made of a number of small crystals of the drug, having properties adequate for direct compression when manufacturing tablets, the link between the process and these properties has to be made. They identified the steps occurring in the process, including the formation of an emulsion whose droplets are made of drug dissolved in a solvent, the creation of the supersaturation of the drug in the droplets by mass transfer and nucleation, growth and agglomeration of drug crystals inside the droplets.

2.5 Process control

The objectives of pharmaceutical crystallization process control may include: (1) identifying crystallization process end-point for phase composition and polymorphism control (Norris, *et al*., 1997) ; (2) establishing crystallization process window (Guan and Pitchumani, 2004) so as to control crystal habits, morphology, and other physico-chemical properties of crystals; (3) Effective strategies to monitor and control the degree of supersaturation (Févotte, 2002) so desired process thermodynamics and kinetics can be attained; (4) structured approach to acquire the experimental data of the crystallization according to DOE, then optimizing the process within the design space for best possible outcomes (Chung, *et al*., 2000), etc. Unfortunately, not many online system and advanced control strategies have been implemented for pharmaceutical crystallization process so far.

Ultrasonics example For a nondestructive detection of the solid-liquid interface during crystallization process of metallic alloys, ultrasonic pulse-echo methods was used (Parker, *et al*., 1985). Based on the time-of-flight of the echo signal reflected at the solid-liquid interface and the ultrasonic velocity in the transport medium, the position, and subsequently the velocity, of the moving interface can be determined. The developed real-time signal evaluation can be used to control the movement of the sample relative to the furnace during directional solidification (Schmachtl, *et al.*, 1998).

Close-loop control example A simple example from the semiconductor industry is the closed-loop feedback control in solidification process (Parker, 1982). The dislocation-free single crystal ingots of silicon, 3" in diameter and several feet long, are routinely grown using the Czochraski or "crystal pulling" process. The closed-loop feedback control produces a constant diameter ingot as it is pulled from the crucible of molten silicon. This is not an

easy task as the heat flow in both crucible and crystal is continuously changing as the liquid level drops and the ingot lengthens. The constant diameter feature is of critical importance not only for ease of subsequent processing into wafers and chips, but also because diameter changes can make it difficult to produce a dislocation-free ingot. The basic control signal is appropriately processed to produce constant diameter by varying the pull rate or melt temperature.

Adaptive control examples An adaptive control system is one in which the controller parameters are adjusted automatically to compensate for changing process conditions (Seborg, *et al*., 1989). Adaptive control techniques are applicable to most pharmaceutical crystallization processes due to their nonlinear characteristics of nucleation and crystal growth. However, tracking of various temperature setpoint trajectories appears to be a very difficult task if the crystallizer is cooled through vacuum, and advanced closed-loop control strategies have to be considered. Févotte and Klein (1993) used so called partial state model reference generalized predictive control approach (PSMR GPC) to the crystallization of organic compounds.

3. USE OF PAT FOR API CRYSTALLIZATION PROCESS CONTROL: A KNOWLEDGED-BASED AND SYSTEMS APPROACH

In the book by Randolph and Larson (1988), the information flow diagram highlighted complex feedback interaction of various crystallization factors. To be able to make accurate prediction and execute excellent process control, a knowledge-based and systems approach is much needed. The FDA defines PAT to be "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." (FDA PAT Guidance, 2004). Safety, efficacy, and quality are three key elements for FDA's regulation of drug substances and drug products. Effective and efficient utilization of the body of scientific knowledge in a structured manner would be encouraged at the PAT domain. As such, a conceptual PAT framework that fully utilizes the accumulated scientific knowledge for API crystallization process control may be outlined here:

(1) product/process design based on fundamental understanding of the crystallization process, including thermodynamics, kinetics, polymorphism, CSD and crystal shape, etc.
(2) using design of experiment (DOE) and other statistical methodologies to identify critical process variables and possible interactions among in-coming materials properties, process variables, and crystal product quality attributes
(3) using modeling approaches to establish multivariate correlation, causal link, and mechanistic understanding of the crystallization process
(4) at the system level, design and implement a control strategy that can accommodate and/or compensate inevitable variability of in-coming materials and process variables such that consistent high quality of crystal products can be achieved. This control strategy may also include on-line or near real-time process/product characterization. The quality attributes of the crystallization process and associated drug substances should include the following:
(a) consistent crystal/particle properties within boundary; (b) optimized process efficiency; (c) consistent bulk powder properties within boundary such as flowability and compactibility; (d) consistent product performance such as bioavailability, potency and dissolution rate.

4. HYPOTHETICAL CASE STUDIES OF USING PAT FOR PHARMACEUTICAL CRYSTALLIZATION PROCESS CONTROL

Given the scientific progress in the crystallization area over the last two decades, some of hypothetical case studies may be articulated below to illustrate a few key elements of the PAT framework for API crystallization process control.

4.1. In-situ monitoring polymorphism and process end-point

Progesterone is known to exist in five polymorphs with forms I and II being the two relevant forms in the crystallization studies. In-situ Raman spectroscopy has been used to monitor progesterone polymorph transformation for a post-crystallization slurry (Wang, *et al*, 2000). From II is the kinetically favored polymorph formed during isothermal crystallization, Form I is the thermodynamically favored polymorph produced following stirring of the crystalline slurry. Turnover kinetics for this polymorphic transformation were obtained over wide process conditions (such as transformation time, temperature, etc.) such that a suitable process window (process parameters, cycle time) at Pharmacia was established to enable its manufacture to consistently and reliably produce either of two desired progesterone polymorphs.

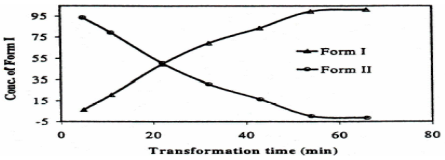

Fig. 1. Progesterone polymorph conversion profile (Wang *et al*, 2000. Reproduced with permission of the American Chemical Society)

4.2. Using ANNs and Knowledge-based hybrid (KBH) modeling for system control

Artificial neural networks (ANNs) have been used to predict significant covariants for population pharmacokinetic and pharmacodynamic (PK/PD) modeling (Haidar *et al*, 2002), and to rank relative importance of various formulation and process factors governing the in-vitro dissolution from enteric-coated sustained release (SR) minitablets (Leane, *et al*, 2003). ANNs were also evaluated in a knowledge-based hybrid (KBH) modeling framework for batch sugar crystallization process by Azevedo's group (Georgieva *et al*, 2003), as illustrated below.

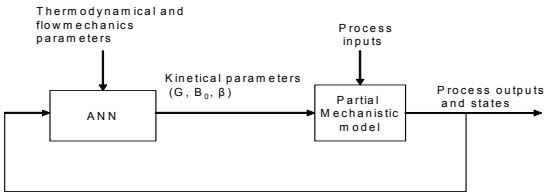

Fig. 2. KBH model structure (Georgieva *et al*, 2003. Reproduced with the permission from Elsevier)

The mechanistic part includes mass balance, energy balance, population balance, and also crystallization kinetic parameters equation. ANN represents the kinetic parameters (G, B_0, β) in the framework of the overall process model, coupled with the correlations for the physical properties of the materials involved. The on-line measurement of the crystallization system provides data for hybrid ANN training and sensitivity analysis. Model validation was done through analysis of process outputs along operation. The benefits of using KBH model to accurately predict CSD in this case could be summarized as: a better understanding of the sugar crystallization phenomena, optimizing the manipulated input time profiles, and obtaining sugar crystals with desired quality characteristics.

4.3. First principle and direct design

A recent review by Braatz's group discussed the first-principles and direct design approaches for the control of pharmaceutical crystallization (Fujiwara *et al*, 2005). An iterative procedure involving optimal experimental design, automated batch experiments, parameter estimation, and model selection was proposed. This procedure has been applied to various crystallization processes including those with shape changes and to pharmaceuticals.

5. CONCLUDING REMARKS

Under the FDA PAT Framework, for the pharmaceutical API crystallization process, process understanding, process/product design and control through knowledge-based and systems approach could help to accurately predict process outcomes, to execute precise process control, and to ensure consistently deliver high quality of crystals within process boundary. Once these are done, regulatory relief will be attainable, since the science behind the process development, scale-up, and manufacturing already proactively address the issues that could lead poor product quality, thus the risks to the drug substances and drug products would have been eliminated or mitigated through process understanding.

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

REFERENCES

Alamdari, A. and Tabkhi, F., "Kinetics of hexamine crystallization in industrial scale", *Chem. Eng. and Processing*, **43**, p. 803-810 (2004)

Chung, S. H., *et al*., "Optimal model-based experimental design in batch crystallization", *Chemo. Int. Lab. Sys.*, **50**, p. 83-90 (2000)

Damian, F., *et al*., "Thermal characterization of the antiviral drug UC-781 and stability of its glass", *Thermochimica Acta*, **366**, p. 61-69 (2001)

Espitalier, F., *et al*., "Particle design Part A: Nucleation kinetics of ketoprofen", *Chem. Eng. J.* , **68**, p. 95-102 (1997)

Espitalier, F., *et al*., "Particle design Part B: batch quasi-emulsion process and mechanism of grain formation of ketoprofen", *Chem. Eng. J.*, **68**, p. 103-114 (1997)

Faure, A., *et al*., "Process control and scale-up of pharmaceutical wet granulation processes", *Eur. J. Pharm. Biopharm.*, **52**, p. 269-277 (2001)

FDA Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. http://www.fda.gov/cder/guidance/6419fnl.pdf

Févotte, G. and Klein, J. P., "Predictive temperature tracking for batch evaporative crystallizers: the partial state model reference approach", *J. Pro. Control*, **3**(4), p. 225-232 (1993)

Févotte, G., "New perspectives for the on-line monitoring of pharmaceutical crystallization processes using in situ infrared spectroscopy", *Int. J. of Pharm.*, **241**, p. 263-278 (2002)

Fevotte, G., *et al*., "Applications of NIR spectroscopy to monitoring and analyzing the solid state during industrial crystallization processes", *Int. J. Pharm.*, **273**, p. 159-169 (2004)

Fujiwara, M., *et al*, "First-principles and direct design

approaches for the control of pharmaceutical crystallization", *J. Pro. Control*, **15**, p. 493-504 (2005)

Gandhi, R. B., *et al*., "Pharmaceutical relationships of three solid state forms of stavudine", *Int. J. Pharm.*, **201**, p. 221-237 (2000)

Eric Garcia, E., *et al*., "Dissolution and phase transition of pharmaceutical compounds", *J. Cry. Grow*., **237-239**, p. 2233-2239 (2002)

Georgieeva, P., *et al*., "Knowledged-based hybrid modeling of a batch crystallization when accounting for nucleation, growth and agglomeration phenomena", *Chem. Eng. Sci.*, **58**, p. 3699-3713 (2003)

Guan, X. and Pitchumani, "Modeling of spherulitic crystallization in thermoplastic tow-placement process: heat transfer analysis", *Comp. Sci. Tech.*, **64**, p. 1123-1134 (2004)

Haidar, S. H., *et al*, "Modeling the pharmacokinetics and pharmacodynamics of a unique oral hypoglycemic agent using neural networks,"*Pharm. Res.*, **19** (1), p. 87-91 (2002)

Hornedo, N. R. and Murphy,D., "Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems", *J. Pharm. Sci.*, **88** (7), p. 651-660 (1999)

Leane, M. M., *et al*, "The Use of Artificial Neural Networks for the Selection of the Most Appropriate Formulation and Processing Variables in Order to Predict the In Vitro Dissolution of Sustained Release Minitablets", *AAPS PharmSciTech* 2003; **4**(2) Article 26.

Meadhra, R. Ó.and Rosmalen, G. M. V., "Scale-up of Ammonium Sulphate Crystallization in A DTB Crystallizer", *Chem. Eng. Sci*., **51**, p. 3943-3950 (1996)

Miletic, I., *et al.*, "An industrial perspective on implementing on-line applications of multivariate statistics", *J. Pro. Control*, **14**, p. 821-836 (2004)

Murphy, D., *et al*., "Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and effect of lattice disorder", *Int. J. of Pharm.*, **246**, p. 121-134 (2002)

Monnier, O., *et al*., "Model identification of batch cooling crystallization through calorimetry and image analysis", *Chem. Eng. Sci.*, **52**, p. 1125-1139 (1997)

Norris, T., et al., "Determination of End-points for Polymorph Conversations of Crsyalline Organic Compounds Using On-line Near-infrared Spectroscopy", *The Analyst*, **12**, p. 549-552 (1997)

R. L. Parker, R. L., "Ultrasonic measurement of solid/liquid interface position during solidification and melting of metals", *AIP Conf. Pro.*, Issue 84, p. 254-271 (1982)

Parker, R. L.,*et al*., "Application of pulse-echo ultrasonics to locate the solid/liquid interface during solidification and melting of steel and other metals", *J. Appl. Physics*, **58**(11), p. 4150-4164 (1985)

Peres, J. *et al*, "Knowledge based modular networks for process modeling and control", *Comp. Chem. Eng.*, **25**, p. 783-791 (2001)

F. Puel, F., *et al*., "Simulation and analysis of industrial crystallization processes through multidimensional population balance equations. Part 1: a resolution algorithm based on the method of classes", *Chem. Eng. Sci.*, **58**, p. 3715-3727 (2003)

Randolph, A.D. and Larson, M. A. *Theory of Particulate Processes*, 2nd ed., Academic Press, New York, NY (1988)

Seborg, D. E., *et al*., *Process Dynamics and Control*, John Wiley & Sons, New York, NY (1989)

Schmachtl, M., *et al*., "Crystallization process control during directional solidification in a high-temperature-gradient furnace by guided ultrasonic waves and real-time signal evaluation", *Ultrasonics*, **36**, p. 291-295 (1998)

Starbuck, C., *et al*., "Process Optimization of a Complex Pharmaceutical Ploymorphic System via In Situ Raman Spectroscopy", *Crystal Growth & Design*, **2** (6), p. 515-522 (2002)

Stephenson, G. A., *et al*., "Characterization of the solid state: quantative issues", *Adv. Drug Delivery Reviews*, **48**, p. 67-90 (2001)

Taday, P. F., *et al*., "Using Terahertz Pulse Spectroscopy to Study the Crystalline Structure of a Drug: A Case Study of the Ploymorphs of Rantidine Hydrochloride", *Journal of Pharmaceutical Sciences*, **92**(4), p. 831-837 (2003)

Togkalidou, T., *et al*., "Experimental Design and Inferential Modeling in Pharmaceutical Crystallization", *AIChE Journal*, **47**(1), p. 160-168 (2001)

Joachim Ulrich, J., and Strege, C., "Some aspects of the importance of metastable zone width and nucleation in industrial crystallizers", *Journal of Crystal Growth*, **237-239**, p. 2130-2135 (2002)

Wang, F., *et al*., "An investigation of the solvent-mediated polymorphic transformation progesterone using in situ Raman spectroscopy", *Org. Process Res. Dev.*, **4**, p. 391-395 (2000)

Wynm E. J. W. and Hounslow, M. J., "Integral population balance equations for growth", *Chemical Engineering Science*, **52**(5), p. 733-746 (1997)

Yu, L., *et al*., "Physical characterization of polymorphic drugs: an integrated characterization strategy", *Pharm. Sci. & Tech. Today*, **1**(3), p. 118-127 (1998)