Innovative crystallization of drugs using PAT technology

Theses of PhD dissertation

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1. Introduction

Crystallization, which is the last step of the drug synthesis, determines the physical and chemical properties of the drugs. Approximately 90% of the commercially available drugs (e.g. tablets, aerosol, capsules, and suspensions) contain crystalline active pharmaceutical ingredient. The average production cost of a drug batch is around 100 E USD but it can reach 1-2 M USD [1]. Accidental mistakes can increase significantly the costs of production; consequently the crystallization has considerable effect on the pharmaceutical efficiency and also profitableness. The chemical (neutral or salt form, purity) and physical (polymorphism, particle size, particle size distribution, crystal shape) properties of the drug have critical role in the efficiency of the crystalline material (bioavailability, tablet stability, or toxicity) or in the effective processing steps of the production (filtration, drying). Purposeful modification of these drug properties allows simple formulation of the drug with improved solubility, maximizing the therapeutic effect and simultaneously reducing the product side effects to minimum. Development of the technology has also become a critical factor since the generic drugs require low-cost production procedure. Thus improvement of crystallization control allows realizing excellent product quality and effective production. Furthermore it can increase significantly the quality of human life bringing new drugs faster and cheaper into market.

2. Literature and aims

The conventional drug production steps (synthesis $\rightarrow$ crystallization $\rightarrow$ filtration $\rightarrow$ drying $\rightarrow$ granulation $\rightarrow$ drying $\rightarrow$ blending $\rightarrow$ tableting) are time and energy consuming processes. Therefore an important aim is to make the whole production simpler and crystallize direct compressible drugs facilitating the formulation procedure. In such cases, the granulation and subsequent drying process can be omitted thus production time and costs or the space requirements can be reduced. In many cases the traditional crystallizations are not suitable to ensure the desired product morphology, therefore application of additional processing steps (such as milling) become necessary, which would cause chemical degradation of the crystalline drugs. The purposeful application of excipients of formulation in the crystallization

processes has recently appeared in the literature as a new alternative way. The exact role of these additives in the crystallization mechanism is still debatable, however, promising results encourage performing further research work in this area in order to crystallize directly compressible active pharmaceutical ingredients. Moreover in order to apply Process Analytical Technologies (PAT) it is essential to design the end product properties by using simultaneous analysis, control and improvement of crystallization processes. Real-time analytical monitoring help to understand the mechanism of crystallization makes clear the effect of additives and allows the accurate process control. In spite of its effectiveness scientific publication (independent of us) for controlling polymorphism with in-line Raman spectroscopy has not yet published until now. Therefore real-time Raman spectroscopy has been used to monitor our crystallization experiments. Earlier Raman spectroscopy was applied successfully for monitoring formulation technology quantifying this way chemical change in the drugs. Effective real-time Raman controlling would be particularly important to ensure the desired product quality during continuous technologies (ie: extrusion, electrospinning), which ones are also preferred by the pharmaceutical authorities.

The objectives of the experimental work, based on the literature, can be summarized into three main points:

- Building modern controlled laboratory reactor system to perform various pharmaceutical crystallizations,
- Purposeful application of formulation excipients during drug crystallizations, mapping their effects on the process kinetics and product morphology, establishing general trends,
- Monitoring crystallization and other formulation technology (ie. extrusion, electrospinning) with in-line Raman spectroscopy, feedback controlling of the processes with the aid of real-time Raman information.

The precise knowledge of the controlled laboratory reactor system was essential to develop the Raman based PAT technology. Accordingly, the process controlled laboratory system has developed considering user requirements or the opportunity to further innovations and optimizations.

Firstly the effect of various additives was studied during cooling crystallization of carvedilol of poor flowability. Mainly the nature and power of additive effects were examined with excipients screening.

We tried to explain the effects and mechanism of one favorable additive using it in other crystallization method (antisolvent combined cooling crystallization) and monitoring the
process by in-line non invasive Raman spectroscopy. Cooling crystallization of Famotidine and Donepezil HCl were performed to clarify the effect of additive concentration and molecular weight as well. Thermodynamic relationship of carvedilol polymorphs were studied during cooling crystallization and solvent mediated polymorphic transition of carvedilol with the aid of real-time Raman monitoring. Another aim was to develop a Raman based PAT system, which make the production of a desired polymorph possible despite of disturbing factors. The method of Raman monitoring was selected to apply controlled continuous formulation processes (ie. extrusion, electrospinning) in order to ensure product quality.

3. Applied methods

3.1. Experimental methods

**Crystallization**
150 ml, 1000 ml glass reactor
Stardom process controller software (PLC)
Labram dispersion Raman spectrometer with optical fibre coupled Raman probe

**Extrusion**
HAAKE Minilab twin screw extuder

**Electrospinning**
NT-35 high voltage supply
SEP-10S syringe pump

3.2. Characterization methods

**Raman spectroscopy**
Horiba Jobin Yvon Labram Raman spectrocope

**X-ray powder diffraction (XRPD)**
X’Pert Pro MDP, PANalytical X-ray powder diffractometer
Polarization light microscope
Carl Zeiss Jena AMPLIVAL polarization microscope

Scanning electron microscope (SEM)
JEOL JSM-5500 LV Scanning electron microscope

Laser diffraction crystal size analyzer
HELOS KR Sympatec laser size analyzer

$^1$H-NMR
Bruker Avance-500 $^1$H-NMR spectroscope

Dissolution test
ERWEKA DT6 dissolution tester

Flowability measurements
Erweka SVM 12 compaction tester

Tableting
Dott Bonapace CPR-6 eccentric tablet machine
Schleuniger-4M tablet strength tester

4. Theses

1. The increasing crystallization inhibition effect of polyvinyl-pyrrolidone as a function of additive molecular weight was studied with in-line non-invasive Raman spectroscopy during cooling crystallization of carvedilol, famitidine and donepezil HCl drugs. The crystal growth orienting effect of polyvinyl-pyrrolidone depended on the molecular weight of polymer and the number of statistical netpoints between the polymer chains in solution, moreover in the case of strong drug-additive interactions the polymer facilitates the formation of excellent flow crystalline powder. [XII, XIII]
2. Directly compressible generic tablets were produced in the presence of a few amount polyvinyl-pyrrolidone during antisolvent combined cooling crystallization of carvedilol ensuring the same dissolution profile of the drug. PVP-K12 and PVP-K90 were the most effective crystal habit modifier. Real-time Raman spectroscopy studies – in harmony with the results of quantum chemical calculations – have confirmed that Form III polymorph is thermodynamically stable under experimental circumstances, new procedure was developed to monitor the transformation from the kinetically preferred Form II polymorph to the thermodinamically stable Form III hemihydrate form. [III, 13]

3. Thermo-dynamically stable famotidine Form A polymorph was produced with a few amount of polyvinyl-pyrrolidone (PVP-K12, PVP-K30, PVP-K90) in cooling crystallization, the products could be characterized as excellent flow crystal aggregates. Increasing the molecular weight and the concentration of the polyvinyl-pyrrolidone resulted in the formation of two fractions of drug particles due to secondary nucleation. The quantity of the smaller fraction was increased as a function of increasing polymer concentration. [14]

4. Solvent mediated polymorphic transitions and cooling crystallizations of carvedilol were monitored first time by in-line Raman spectroscopy. The thermodynamic relationships between the forms of carvedilol were studied at different temperatures and drug concentrations and evaluated by chemometric methods. A number of new unstable solvate formation was detected in solution, moreover a new Form V* “channel solvate” was also prepared in ethyl-acetate whose thermal stability were analyzed under different drying conditions by Raman, XRPD and $^1$H-NMR measurements. [I, IV, VII]

5. Raman signal feedback control was first realized to control crystallization according to the latest trends of pharmaceutical science, which can be characterized as a promising PAT technology. The effectiveness of the feedback control was tested by disturbing effects (in the presence of polymorph impurity). The results confirmed that the control algorithm can ensure the desired product morphology even in the presence of a few amount undesired polymorph. The feedback control, considering direct intensities, can be applied successfully in crystallizations associations with changes in particle size. [II, 15]

6. Real-time Raman spectroscopy was used first to determine the drug morphology during continuous electrospinning technology. The analysis of the drug morphology was performed
directly from the in-line non-invasively recorded Raman intensity value owning to the thickness calibration of the nanofiber layer. Moreover process classification was also executed with the aid of the control of nanofiber layer thickness. [V, VIII, IX, X, 17]

5. Application possibilities

Formulation properties of drugs can be improved using a few amounts of additives during these new kind of crystallizations. Treated crystalline products with excellent flowability make the manufacturing technology economical and simpler than the traditionally formulation steps (milling, granulation, drying). Real-time Raman spectroscopy turned to be an effective tool to explore the impact of the additives and to understand the crystallization processes. The developed feedback control based on the Raman signal intensity changes has a great importance in the pharmaceutical industry in harmony with the latest regulation official forecasts. The development regarding the famotidine can mean significant advancement in the technology of Richter Gedeon Pharmaceutical Company, while the results regarding real time Raman monitoring has been utilized by EGIS Company, having such a sensor installed.

6. Publications

*Scientific publications in the journals with impact factor:*

X. Z.K. Nagy, A. Balogh, G. Drávavölgyi, J. Ferguson, H. Pataki, B. Vajna, G. Marosi Solvent-free melt electrospinning for preparation of fast dissolving drug delivery system and comparison with solvent-based
electrospun and melt extruded systems. *Journal of Pharmaceutical Sciences* 2013, 102 (2), 508-517. IF: 3.055 I:1


*Scientific publications in the journals without impact factor:*


Oral presentations:

1. H. Pataki: Raman módszer alkalmazása gyógyszer kristályosítás monitorozására, Pannon Tudományok Akadémia rendezvénye, 2009, Balatonalmádi

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