ABSTRACT

Optimization of the crystallization of active pharmaceutical ingredients by using in-situ analytical techniques

The process of obtaining the active pharmaceutical ingredient ticagrelor is complex and consists of several synthesis steps, including crystallization for chemical purification of the product in the penultimate step and recrystallization in the final step for the design of the physical properties of the product. The development, research and design of the crystallization is a crucial step in preparing both appropriate chemical and physical properties of the product, including polymorphic form, morphology and particle size. Yield, filtration, drying of the product, stability, scaling up of the process on the pilot scale or industrial scale represent challenges in the development and design of the crystallization process. The purpose of this work is to combine theoretical knowledge of crystallization with practical performance. The goal is to optimize, define and variate the process parameters of crystallization to prepare a product with favourable physical properties in the penultimate process step of chemical purification in chosen solvent and antisolvent and to omit the last recrystallization step. To optimize, control and design the crystallization process, to manipulate of the physical properties through nucleation and crystal growth in the penultimate process step and to improve production costs, solubility diagrams in the chosen system of solvent and antisolvent were prepared and the phase diagram of the polymorphic forms, which represents enantiotropic relations between them, transition points and defines stability at chosen temperature. The crucial process parameters, essential for spontaneous crystallization, seeding crystallization and ultrasound-assisted crystallization were extensively studied while the pros and cons of each were adequately exposed. Special attention was given to produced product with pure polymorphic form, especially product of favourable polymorphic form II, or product with pure polymorphic form I or III, which will be used as an input material for next recrystallization process step. Polymorphic forms I and III were prepared with spontaneous crystallization, in which the nucleation occurs on an uncontrollable way, is time-consuming process to prepare polymorphic form III and unable to produce stable polymorphic form II. The product produced with spontaneous crystallization can have unwanted variability in physical properties. Better results were achieved with seeding crystallization, with which all three polymorphic forms I, II and III were produced, with wider particle size distribution and a high level of agglomerates. Thus, additional energy and a time-consuming process of deagglomeration or milling is needed. In contrast, with ultrasound-assisted crystallization, all three polymorphic forms of ticagrelor were produced faster than in the case of conventional crystallization. A high quality product was achieved with a narrow particle size distribution, uniform morphology and reduced agglomeration. Ultrasound-assisted crystallization significantly improved fundamental crystallization parameters: nucleation, crystal growth and production time. The seed preparation, analysis and storage of the seed can be omitted. With the optimization of process

parameters and based on the research and gained knowledge, the polymorphic form II was produced as a favourable form in the penultimate crystallization process step, without additional deagglomeration step. The last process step of recrystallization can be omitted. As a result, repeatable, robust, optimized and controllable crystallization was developed, which provides repeatable physical properties of drug učinkovine ticagrelor and represents the possibility for successfully scaled-up on pilot or industrial scale. Improved cost effectiveness of the production of active pharmaceutical ingredient provides better competition on market and for the patient more affordable as well as safe, effective and high quality drug product.

Keywords: active pharmaceutical ingredient ticagrelor, crystallization, polymorphic form, morphology, particle size