ABSTRACT

Prevalence and importance of polymorphism occurring in pharmaceutical compounds are well recognized. It is of great importance to prepare and select the right form from the beginning, during drug discovery development and throughout the shelf life of drug product. Patent protection of innovating company for a new crystalline form of a compound can be extremely valuable. However, the failure in polymorph screening strategy can open the possible route for generic companies, especially when the new form possesses a desirable physical properties.

Polymorph screening is then an important stage in the drug development process and consists of an integral part of new chemical entity (NCE) development. The investigation of possible solid forms of a NCE should be carried out as early in the development process (preclinical) as to the 2nd and 3rd phase. The search for new solid forms involves performing a large number of experiments, analysis and interpretation of their results. Conventional screening method required even several tens or hundreds of crystallization experiments. Developing and implementation of a new and fast method of new solid state forms searching will cause considerable simplification of the procedure of active pharmaceutical ingredients (APIs) development, additionally saving the time consumed in development stage.

Continuous efforts of pharmaceutical companies to reduce the costs of the drug substance production tends to continuing search for a new molecules with improved physicochemical properties that will not earn technological problems, simultaneously exhibiting the same both chemical and physical stability. For generic drug companies is important to achieve API modification with improved physicochemical properties (especially having a greater solubility in water).

The main aim of this work was to select and prepare a new solid state forms of active pharmaceutical substances that exhibit improved therapeutic properties. Usually, more favorable bioavailability is achieved through enhancing the solubility. As a model substance baclofen was selected, in case of which two polymorphs, monohydrate and hydrochloride salt (reported in the patent and scientific literature) are approved for therapeutic usage (and a few not approved forms). Crystallization of baclofen carries some technological complications, it also shows low solubility in water.

The studies carried out in this doctoral dissertation were focused on searching for the new solid state form of baclofen appropriates more favorable physicochemical properties. Therefore, the work was focused on the search of the novel polymorph screening technique, which allows to find a material with the desired properties in an accurate and a fast way. In this doctoral dissertation the methods of new crystalline forms predicting and screening in a timely and cost-effective manner using computer tools (Polymorph Predictor) and grinding of the active substance with (SDG - Solvent Drop Grinding) and without the solvent addition method were described.

In the theoretical part of the doctoral dissertation solid state forms of API were characterized and the interactions occurring between the molecules building them were described. An extensive chapter is devoted to the phenomenon of active substances polymorphism and focused on understanding their interrelationships and transformations. Crystallization process as a key stages of deciding on subsequent physicochemical property

APIs was also mentioned. In a separate chapter the basics dissolving of solids were also explained. The paper presents a detailed review of the literature on improving the physicochemical properties of the substance and methods of searching for a new form of API. In addition, thesis presents the physicochemical methods of characterization and testing of solid state forms of pharmaceuticals. Particular attention was paid on polymorphism phenomenon and polymorph transformations.

In the experimental part of the thesis the starting materials used in synthesis and crystallization were characterized and method for new solid forms of baclofen preparation was described. New solid state forms of baclofen were analyzed by different analytic techniques like: single crystal X-ray diffraction, X-ray powder diffraction technique (XRPD), differential scanning calorimetry (DSC), infra-red spectroscopy (IR) and high-performance liquid chromatography (HPLC). Described in literature HPLC method for purity assessment of baclofen was modified for the quantitive solubility analysis in intrinsic media purpose.

Besides theoretical aspects, the issues covered by this dissertation also have very practical importance. In the context of the doctoral dissertation, a new strategy to unknown solid state forms of API screening and the methods for their preparation were revealed. Application of wet grinding as a tool for searching of promising systems for new cocrystal or salt preparation was really helpful in determining of baclofen-excipient (component) systems for further crystallization experiments. Novel strategy described in the thesis allows on significantly simplification of the new active substances forms finding process and at the same time reducing the solvents usage and because of that it is an interesting alternative to standard screening methods.

Described in the thesis strategy for new solid state forms of API screening has proven to be effective and allowed to obtain and complete characterize of the new 8 solid state forms baclofen. The resulting substances frequently had significantly more favorable physicochemical properties of both solubility and technological properties.

Keywords: polymorphism, baclofen, new solid state of API screening, solubility enhancement