International Journal of Pharmaceutics 547 (2018) 404–420

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Pharmaceutical cocrystallization techniques. Advances and challenges

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ARTICLE INFO

Keywords:
Cocrystals
Cocrystallization methods
Solvent-based
Solvent-free
Screening methods
Industrial production
Continuous production
Process analytical technology

ABSTRACT

Cocrystals are homogenous (single-phase) crystalline structures composed by two or more components in a definite stoichiometric ratio bonded together by noncovalent bonds. Pharmaceutical industry has been showing interest in cocrystals due to their ability to improve active pharmaceutical ingredients (API's) properties, such as solubility, dissolution, bioavailability, stability and processability. The necessity for high-throughput screening methods and methods capable of producing cocrystals in an industrial scale still hinders the use of cocrystals by the pharmaceutical industry.

The aim of this review is to present an extensive overview of the cocrystallization methods, focusing in the specificities of each technique, its advantages and disadvantages. The review is divided into solvent-based and solvent-free methods. The most appropriate methods to the different stages of cocrystals manufacture, from the screening phase to industrial production are identified. The use of continuous and scalable methods in cocrystal production as well as the implementation of quality-by-design and process analytical technology concepts are also addressed.

1. Introduction

The development of a new medicinal product from a novel compound (either synthesized, retrieved from a natural source or produced by biotechnological pathways) is a complex procedure that can be subdivided into five distinct stages: strategic research, exploratory research, candidate drug selection, exploratory development and full development. There is a shift in the pharmaceutical industry to a rational drug design and development in which the R&D departments have interdisciplinary teams to develop increase knowledge regarding the new drug. However, in some cases "trial-and-error" approaches are still used, where a molecule is passed through development stages until it meets a limited set of criteria with little contribution from other functional areas. As so, drug candidates often advance to human trials without sufficient information on potential crystal forms, physical properties and manufacturing capabilities. Consequently, the lack of full characterization of the drug candidate through multiple perspectives traditionally leads to empirically, complex and costly problems on late stages of development, which could be early avoided (Chow et al., 2008). In the present context of paradigm shift imposed by the regulatory entities where risk knowledge and management approaches are paramount so that quality should be built into the drug product from its inception to its full and late development stages.

Given the background, screening and selection of existent solid state of an active pharmaceutical ingredient (API) is one of the most important procedures to be established during early stages of drug development, since it can influence API's physicochemical and mechanical properties and chemical stability, as well as, it can affect its biopharmaceutical properties and manufacturability. Differences between different solid states of the same API merge as a result of discrepancies in molecular interactions, structure, composition and molecular arrangement. (Nanjwade et al., 2011; Sarma et al., 2011)

As solids, API's can exist mainly in two morphological structures: crystalline or amorphous (see Fig. 1).

Pharmaceutical industry prefers crystalline materials due to their characteristics. Crystalline materials are stable and easier to purify, being the main disadvantage their low solubility. On the other side, amorphous forms have a higher energy state and high mobility when compared to crystalline forms, which provide them with higher solubility. However, amorphous materials are less stable and tend to recrystallize over time (Yamamoto et al., 2016).

A pharmaceutical salt is an ionized molecular API (cationic or anionic form) linked to a conterion (molecular or monoatomic) by ionic bonds (Aakeroy et al., 2007; Aitipamula et al., 2012). Salts are widely used in pharmaceutical industry due to the broad capacity to design an API according to desired drug properties. It is estimated that more than 50% of all drug molecules are administered as salts (Serajuddin, 2007). However, salt formation is inadequate for non-ionisable drugs and can

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https://doi.org/10.1016/j.ijpharm.2018.06.024
Received 19 March 2018; Received in revised form 6 June 2018; Accepted 7 June 2018

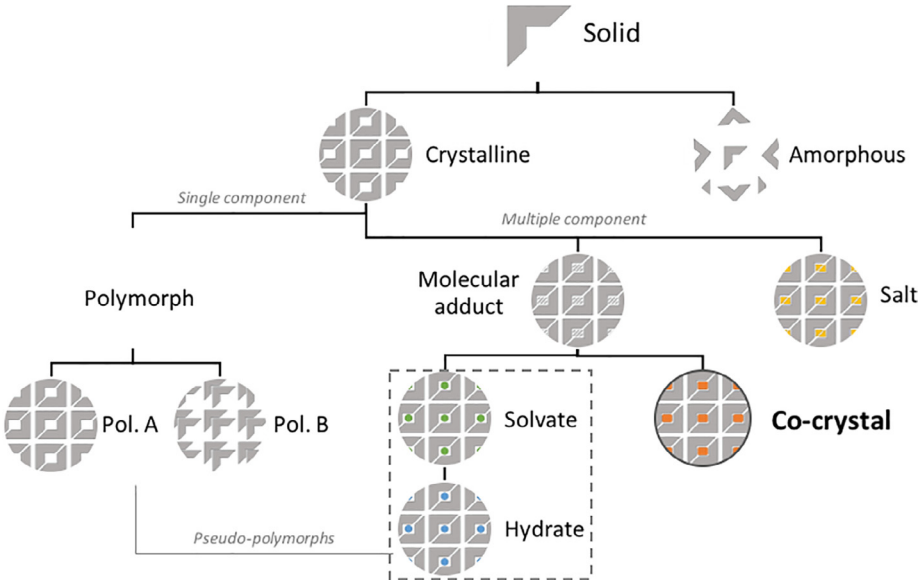

Fig. 1. Schematic representation of API solid forms classification. The solids are divided in to amorphous and crystalline solids. Within the crystalline solids the division is made in single component (polymorphs) and multiple component (molecular adduct and salt). The molecular adduct comprise the solvates/hydrates and cocrystals.

have a number of others disadvantages (Jones et al., 2006; Serajuddin, 2007).

Polymorphism is the ability of a compound to exhibit different stacking arrangements and molecular conformations within the crystal lattice, which means that a compound can exist in various crystalline forms, maintaining the same chemical composition (Aitipamula et al., 2012). Polymorphism is quite common in organic molecules and it is of the upmost importance to screen polymorphs in pharmaceutical applications since not all the polymorphs present the same therapeutic interest (Brittain, 1997). Different polymorphs can have different physicochemical properties such as, packing, melting point, density, crystal shape and kinetic parameters. Besides that, different polymorphs also exhibit different pharmaceutical properties, for example, solubility, bioavailability, stability, hygroscopicity. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product (Aitipamula et al., 2012; Stahly, 2007).

Solvates are defined as crystalline molecular compounds in which molecules of the crystallization solvent are entrapped in the host lattice. If the solvent is water they are called hydrates. The presence of solvent molecules influences the intermolecular interactions and confers different physical (thermodynamic properties) and chemical (solubility, dissolution rate and therefore bioavailability) properties from those of the unsolvated form (Brittain, 1999). Solvates are considered a problem by the pharmaceutical industry since they are unstable and can lose the solvent molecule during processing affecting their physicochemical properties (Aitipamula et al., 2010). Moreover, most solvents used in the API's manufacturing are toxic and should not integrate the final dosage (Jones et al., 2006).

For all the stated reasons, an alternative to polymorphism, salts, solvates and amorphous forms to fine tune API properties would be beneficial to the pharmaceutical industry. Cocrystal appeared as such alternative.

1.1. Cocrystals

Cocrystals definition has been subjected, in the past years, to some disagreement in the scientific community. According to European Medicine Agency (EMA), cocrystals are "homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)" (EMA, 2015).

Cocrystal structure is based in noncovalent interactions between the API and the coformer. The interactions involved are intermolecular interactions, such as van der Waals contact forces, π stacking, hydrogen bonding, electrostatic interaction and halogen bonding between stoichiometric amounts of various molecules. Generally, supramolecular synthons are the used term to refer this basic structural unites within supermolecules. Supramolecular synthons are special arrangements of intermolecular interactions, which can be formed by known feasible operations (Desiraju, 1995). Supramolecular synthons are divided in two groups: homosynthons, which consist in combinations of similar functional groups and, heterosynthons, which are composed by different but complementary functional groups (Hemamalini et al., 2014). Crystal engineering works in this field, recognizing and designing synthons, with the goal of cocrystal rapid development, trying to improve API properties without affecting its intrinsic structure and function. Thus, the alterations are made in crystal packing, by changing the internal arrangement of the molecules, breaking and forming noncovalent bonds. The most common functional groups used for formation of supramolecular synthons by H-bonding are the acid group of carboxylic acids (e.g., acetic acid, benzoic acid, fumaric acid, maleic acid, malonic acid), the amide group (e.g., nicotinamide and urea), the amine group (e.g., benzamide, picolinamide, adenine), and alcohol group (He et al., 2008; Karki et al., 2009).

Both API and coformers can be acid, basic or neutral. In the case of ionic compounds, interactions should remain non-ionic, allowing cocrystal formation and not salt formation (Karki et al., 2009). The proton transfer extent, which depends on pKa values of the compounds, generally dictates the cocrystal formation: if there is no proton transfer, a cocrystal can be formed; if the transfer is complete, a salt is formed (Jones et al., 2006) The Food and Drug Administration (FDA) (Food and Drug Administration, 2016) defined a threshold for the differentiation between salt and cocrystal based on the, ΔpKa. If a cocrystal has ionizable groups, it should be proven that the API and coformer exist in their neutral state in the cocrystal, and interact via nonionic interactions. The FDA states that, when components have a $\Delta pKa \geq 1$, a salt will be formed. If $\Delta pKa < 1$, the complex should be classified as cocrystal. Besides regulatory indications, others have stated a "rule of thumb" that when the ΔpKa is greater than 2.7–3 units, salt formation is expected rather than cocrystal (Cerreia Vioglio et al., 2017). Nevertheless, it is also important to consider crystallization environment. For example, if cocrystallization is developed in organic solvents, pKa values are considerable different from those in water. Consequently, if there is a possibility of salt formation different techniques must be used