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Review

Spring and parachute: How cocrystals enhance solubility

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Abstract

This article is intended to combine literature on cocrystallization – a tool for enhancing the solubility and for improving the physicochemical properties of an API (an API is the molecule which is responsible for providing the therapeutic effect) with special emphasis on the mechanism responsible for the same. The pharmaceutical industries are witnessing a developing crisis in the process of drug development due to the increasing cost of their R&D departments, the failure of some blockbuster drug candidates exhibiting poor aqueous solubility and the unavailability of newer molecules because of patent limitations. Cocrystallization is an emerging approach to improve solubility, dissolution profile, bioavailability, and other physicochemical and mechanical properties of an API. A pharmaceutical cocrystal is now a new epitome which enables the use of a wide range of active pharmaceutical ingredients without the need to form or break the covalent bonds. The prime focus of this review article is the mechanism on how cocrystals have a solubility advantage over the amorphous form. This review also provides a brief introduction to the nature of cocrystals, their role, principles of crystal engineering and also highlights the nature of supramolecular synthons which are present in cocrystals.

Keywords: Cocrystals; Poorly soluble drugs; Spring-parachute phenomena; Solubility

1. Introduction

In the determination of the efficacy as well as the activity of a drug, the solubility and their dissolution rate play pivotal roles. Many of the blockbuster molecules that are discovered have limited application due to their poor solubility and dissolution profiles. The essential challenge for a successful pharmaceutical product developments is to improve the solubility and dissolution profile of poorly soluble drugs without altering their molecular structure [1]. Crystal engineering is a new and an incipient approach to incur a pharmaceutical product having improved physicochemical and mechanical properties. Crystal engineering technologies include formation of cocrystals, metastable polymorphs, high energy amorphous forms and ultrafine particles to ameliorate the properties of an API [2]. The focal point of this review is cocrystals.

In our review of cocrystals it is required to know the fundamental difference between cocrystals and pharmaceutical cocrystal. Cocrystals are structurally homogeneous crystalline materials containing two or more components, present in stoichiometric amount and are discrete neutral molecular reactants which are solid at ambient temperature. Here a pharmaceutical cocrystal means one of the components is an active pharmaceutical ingredient (API), the other components are known as coformers [3] (Fig. 1).

In order to obtain cocrystal, there should be presence of functional group in API and coformers, which have the capability to form either homo or hetero supermolecular synthon. There is formation of non-covalent bonds between an API and coformers and thus the crystal

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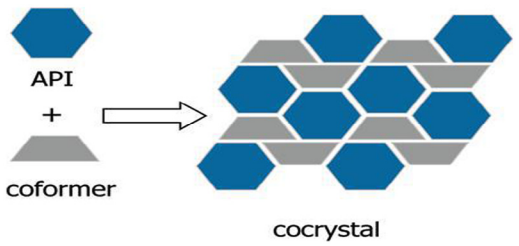

Fig. 1. Multicomponent cocrystal system [4].

lattice is generated repetitively. Pharmacodynamically, coformers provide stability to cocrystals (ballast molecule) while having GRAS (Generally Recognized as Safe) status. Nonetheless even a coformer can be an active molecule that is an active pharmaceutical ingredient. Generally, the ratio of an API and coformer is either 1:1, 1:2, 1:3 or *vice versa* [5]. Bhupinder Singh Sekhon worked on drug-drug cocrystals in which one of the active pharmaceutical ingredients played a role as a coformer [6]. Pharmaceutical cocrystals of non-steroidal anti-inflammatory drugs diflunisal (DIF) and diclofenc (DIC) with theophylline (THP) were obtained by Surov et al. [7].

Advantages of cocrystals: (i) no need to make or break the covalent bonds; (ii) theoretical capability of all type API molecules (weakly ionizable or non-ionizable) to form cocrystals; (iii) stable crystalline form; (iv) presence of numerous potential counter-molecules i.e., coformers like food additives, preservatives, pharmaceutical excipients, and or APIs; and (v) improvement in physicochemical properties as well as pharmacokinetic properties of an API without compromising its pharmacological activity.

2. Pharmaceutical cocrystals – an overview

A pharmaceutical cocrystal is a simple multicomponent system in which at least one of the component is an API in colligation with another type of molecule named coformer which should be non-toxic, having no adverse effects and should be included on the USFDA 'Everything Added to Food in the United States' (EAFUS) list [8]. Cocrystal formation is important to modulate the properties of a drug; moreover it is also useful in the synthesis of NLO (nonlinear optics) materials, designing extended supermolecular architecture, enantioseparation of racemic compounds, etc. [9]. Typically, three steps are involved to design cocrystals:

1. Coformer selection
2. Computational analysis
3. Characterization of cocrystal

For a target API, the coformer/s, which is/are having the ability to interact with the target API via hydrogen bonds should be preferred. Carboxylic acids, amides, and alcohols are found as most common functional groups to interact with each other in cocrystals (Table 1) [11].

As compared to other crystalline forms of APIs, the peculiarity of a cocrystal is that crystal engineering can manipulate these multicomponent systems [12,13]. Crystal engineering entails modification of the crystal packing of a solid material by changing the internal arrangement of the molecules that regulates the breaking and forming of non-covalent bonds (e.g., hydrogen bonding, van der Waals forces, π-stacking, electrostatic interactions).

The most common interaction between an API and a coformer is hydrogen bond formation. The general rules for hydrogen bond are the following [14]:

1. All good proton donors and acceptors are used in hydrogen bonding,
2. If six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds.
3. The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds with one another.

Crystal engineering depends upon the basic principles of supramolecular [3,15] chemistry, chemistry beyond the molecule, in developing novel entities by manipulating the non-covalent intermolecular interactions.

To exemplify this concept, Fig. 2 shows how the crystal packing of carbamazepine (CBZ) has been modified via cocrystallization including hydrogen bond formation with nicotinamide (NIC) which is a coformer [16]. The ratio of CBZ: NIC was 1:1 and the cocrystal was prepared by melting method.

The synthon is a model for the entire crystal structure and is emblematic of the complete crystal. The synthon which appears in a large number of cases wherein a particular set of molecular function is a good or robust synthon [17]. When crystal pattern repeats regularly, the interaction pattern can be called supermolecular synthon. There are two types of supermolecular synthons [18]:

1. Supermolecular Homosynthon
   - It is composed of identical self complementary functionalities.
   - E.g. acid–acid.