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Pharmaceutical Cocrystals

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Abstract

Cocrystals are very interesting and useful product. In this paper the main information about cocrystals is presented. It is shown that cocrystals are solid substances, which consist of few components mixed together. There are a lot of ways of cocrystals production and application. It is shown that cocrystals can be applied in medicine and pharmaceutical industry for improving different properties such as dissolution rate, melting point, solubility, chemical stability etc. Another way of cocrystals application is drug pharmacological action modification.

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Keywords: cocrystals, pharmaceutics, API, crystallization, salt, organic, inorganic, improving of component properties

1. Introduction

The definition of the term "pharmaceutical cocrystal" is still under discussion, but essentially it is a multi-component compound that is formed between a molecular or ionic API (Active Pharmaceutical Ingredience). Cocrystals are solid under ambient conditions (Fig.1). Paul Pfeiffer in his book „*Organische Molekulverbindungen*" (1922, this book were reproducted in 2012 by Publisher: Nabu Press) separated cocrystals into two categories; those made of inorganic:organic components, and those made only of organic components. The inorganic:organic cocrystals include organic molecules cocrystallized with alkali and alkaline earth salts, mineral acids, and halogens as in the case of the halogenated quinones. A majority of the organic:organic cocrystals contained aromatic compounds, with a significant fraction containing di- or trinitro aromatic compounds[1].

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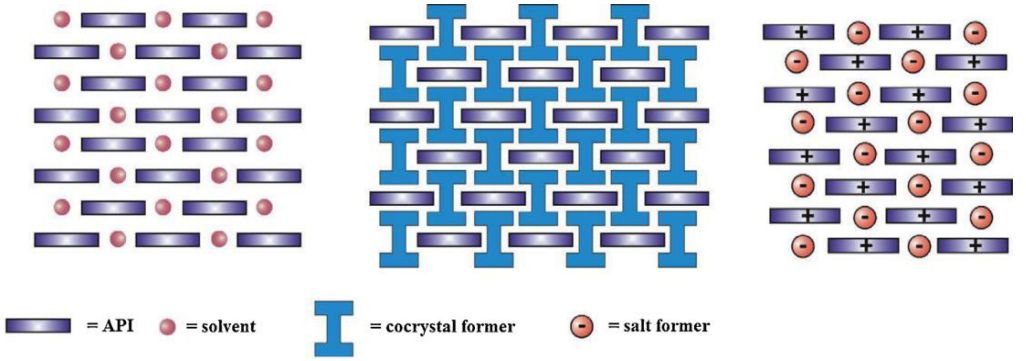

Fig. 1. Schematic representation of API solvates/hydrates, cocrystals and salts[2]

Pharmacodynamically, cocrystal former is a ballast molecule (the same applies to salts), and the GRAS (Generally Recognized as Safe) rules apply. Nevertheless even a cocrystal former can be an active molecule. The stoichiometric ratio of API and cocrystal former in a pharmaceutical cocrystal is mostly simple (1:1, 1:2, 1:3 or *vice versa*). Cocrystals are not necessarily binary compounds, ternary and quarternary cocrystals are known. Cocrystals can be divided into: cocrystal anhydrates, cocrystal hydrates (solvates), cocrystals of salts (unsolvated, unhydrated or solvated, hydrated). The borderline between salts and cocrystals is blurred and can be distinguished by the location of the proton between an acid and a base. In salts, carboxyl proton is moved to the hydrogen of the base while in cocrystals the proton remains on the carboxyl of the acid. In cases when $\Delta pKa = pKa(base) - pKa(acid) = 0 – 3$, the transfer of proton is ambiguous and we talk about the salt-cocrystal continuum.

2. Production

The preparation of cocrystals involves a number of techniques, in gas, liquid or solid phase. The most important is the joint cocrystal growth from solution or joint solid state grinding, often with the addition of a small amount of a "molecular lubricant" (methanol, cyclohexan, chlorophorm etc.), so-called liquid assisted grinding. Furthermore, co-crystals can be synthesized by evaporation, sublimation, melting, sonication etc. It often holds that identical starting components may not yield the same product under different cocrystallization techniques[3].

A multitude of other methods exist in order to produce cocrystals. Crystallizing with a molar excess of one cocrystal former may produce a cocrystal by a decrease in solubility of that one component. Another method to synthesize cocrystals is to conduct the crystallization in a slurry. As with any crystallization, solvent considerations are important. Changing the solvent will change the intermolecular interactions and possibly lead to cocrystal formation. Also, by changing the solvent, phase considerations may be utilized. The role of a solvent in nucleation of cocrystals remains poorly understood but critical in order to obtain a cocrystal from solution[4]. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components. Such properties include melting point, solubility, chemical stability, and mechanical properties.

Some cocrystals have been observed to exist as polymorphs, which may display different physical properties depending on the form of the crystal[5].

As an example of cocrystallization, production of "Coffein citrate" cocrystal is shown on figure 2.

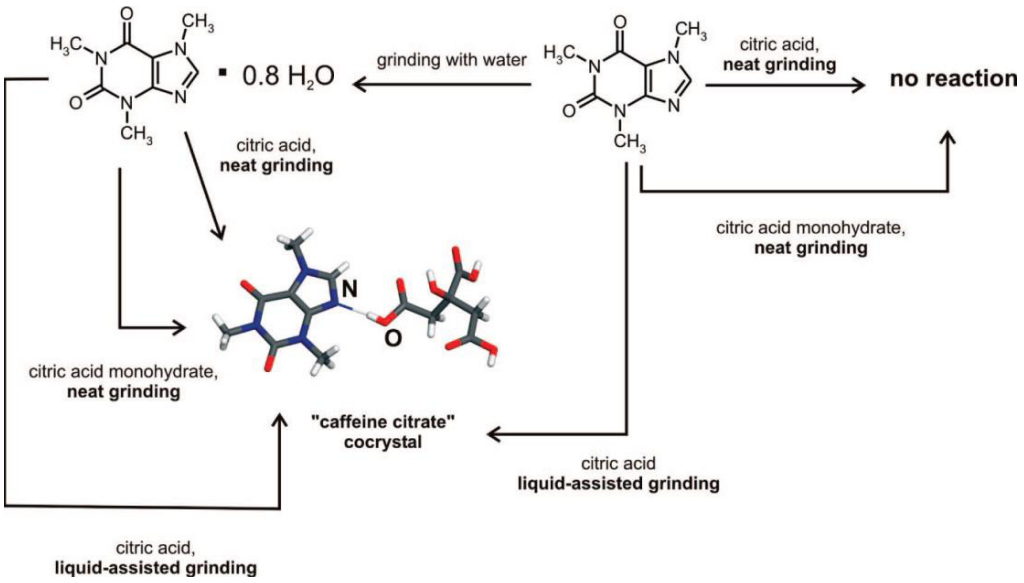

Fig. 2. An overview of solid-state reactions of hydrated and nonhydrated forms of caffeine and citric acid[6]

The cocrystallization potential of some active molecules is studied in detail, e.g. carbamazepine, itraconazole, piroxicam, norfloxacin, fluoxetin, caffein and others. The reason is to achieve a wide variation in solid-state properties of APIs. These efforts stem from principles of supramolecular chemistry and crystal engineering to affect the properties of API through the "bottom up" approach. This is illustrated in the following examples.

By the cocrystallization of antifungal drug itraconazole with 1,4-dicarboxylic acids (succinic acid, L-tartaric acid or L-malic acid) a modification of the dissolution profile is achieved compared to the amorphous form of itraconazole (Sporanox, Janssen-Cilag)[7]. A 1:1 carbamazepine/saccharin cocrystal compared to polymorph III of carbamazepine (anticonvulsant Tegretol, Novartis) shows no polymorphous behaviour and is not prone to hydration[8]. The cocrystallization of pregabalin with S- mandelic acid separates from the mixture of R and S isomers only the (1:1) cocrystal (S)-pregabalin/(S)-mandelic acid. This technology is used by Pfizer in manufacturing dosage form Lyrica[9]. The cocrystals of paracetamol show an improved tablet formation ability than free paracetamol, polymorf I (Panadol, GlaxoSmithKline)[10]. Caffein tends to form hydrates at high RH (relative humidity) while its cocrystals with oxalic acid or malonic acid do not have this unwanted property (never form hydrates)[9]. However, general trends of variation of properties during the transition from APIs to their cocrystals are not so far evident because fundamental causes of cocrystallization are not known so far.

3. Application

A key question concerning the practical application of a cocrystal of a commercial API is whether the cocrystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the cocrystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require. The USA Food and Drug Administration (FDA) have released draft guidance on the regulatory classification of pharmaceutical cocrystals for applicants for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). The FDA defines cocrystals as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" - the implication is that it is two or more types of molecules that are referred to here[11].

The FDA also regards cocrystals as dissociable "API-excipient" complexes, blurring the boundary between cocrystals and physical mixtures. This guidance has generated a strong response from some researchers in the cocrystal field who propose alternative, yet also potentially controversial definitions that distinguish multicomponent APIs and their cocrystals from solvates and hydrates.

Among many recent patents relating to potential commercial cocrystal products, the possibility of combining two active ingredients in a single cocrystal is an interesting one and has been claimed in the cocrystallization of quercetin (a plant-derived flavonoid, used as a nutritional supplement and reputed to offer some anti-cancer properties) with antidiabetic agents such as metformin or tolazamide. The combination drug has been suggested to have physical properties and biological activity that are distinct from the individual properties of the two components. Interesting research pointing the way to applications of cocrystals in the modification of drug pharmacological action has been reported for insulin, a peptide hormone used for the treatment of diabetic patients. Insulin has poor oral bioavailability and is commonly injected. Human insulin has been cocrystallised with a lipophilically modified, closely related insulin analogue octanoyl-N-LysB29-human insulin. The lipophilic formulation was designed to provide a slow release profile compatible with an improved physiological insulin profile[12].

4. Conclusion

Application of pharmaceutical cocrystals is very important alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionizable groups.

Although, the definition of the term “pharmaceutical cocrystal” is still under discussion, it is clear that this substances are very useful, and it is important to explore new cocrystals of an API to improve or obtain some properties, such as habit, bulk density, solubility, compressability, friability, melting point, hygroscopy and dissolution rate.

Another way for cocrystals application is modification of drug pharmacological action, for example insulin. Cocrystals investigation and production are very interesting for researchers and very useful for medics and pharmacologists.

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