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Mini Review

Crystal Engineering Applied to the Development of Novel Pharmaceutical Solid Forms with Improved Bioavailability: the Co Crystals Case

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Abstract

Pharmaceutical co crystal technology has emerged as a promising strategy to enhance bioavailability of poorly water soluble drugs. This mini review presents a brief overview of pharmaceutical co crystals with particular focus on co crystal design, characterization techniques and impacts on drug bioavailability.

Introduction

Active Pharmaceutical Ingredients (APIs) can exist in different crystalline forms and, for this reason, have been subjected to various complications arising from polymorphism, multi component crystals, and amorphous phases [1,2]. One of the straightforward ways to considerably improve the physicochemical and pharmacokinetic properties of an API is to develop novel multi component solid forms, e.g. salts and co crystals. Over the last decade, co crystals have been attracting scientific and pharmaceutical interest due to their potential ability to modify important pharmaceutical properties of APIs such as solubility, dissolution rate, permeability and bioavailability [3,4]. Moreover, co crystal formation show advantages over salts:

A. They do not alter the nature of the API

B. They are not limited to a binary combination (acid-base motif) i.e., area able to address multiple functional groups simultaneously, constituting tertiary and/or quaternary compounds.

Pharmaceutical Co Crystals

Pharmaceutical co crystals are defined as "crystalline single phase materials composed of two or more different molecular compounds generally in a stoichiometric ratio" [3]. Therefore, co crystal is a multiple component crystal stabilized by intermolecular interactions (hydrogen bandings, vander Waals contacts, hydrophobic forces and π-π interactions) between a co crystal former and neutral molecular API. These compounds can also provide a number of crystalline states for a given API without affecting its chemical composition [1-3]. In addition, since co crystals are the result of a supramolecular synthesis (being considered new chemical entities) and their physicochemical and pharmacokinetic properties can be modulated [2,3], they are considerable as a novelty and a non-obvious invention. In legal terms, they can be patentable if they show some utility [5].

Co Crystal Design and Synthesis

The design and synthesis of pharmaceutical co crystals is driven by the crystal engineering principles which states that the properties of the compound depend on the structural arrangement of its molecules in the crystal. From this perspective, modifying its crystal structure by the control over its intermolecular interactions allows to rationalize the design of new crystals exhibiting specific features [6]. First, when we think about co crystal design, a rational planning is required to maximize the probability of API co crystallization. An evaluation of API regarding to the structural motifs, proton transfer (according to pKa) and conformational flexibility is necessary before attempting co crystallization. The presence of functional groups with good hydrogen bond acceptor and donor atoms in the API molecule, which can form robust supramolecular synthons offers a great opportunity to design novel pharmaceutical co crystals [7].

The main steps usually adopted in the search for supramolecular synthons, particularly for the synthesis of co crystals are:

a. Identify in the API molecule the main functional groups.

b. Draw these functional groups separately.

c. Insert these functional groups in systematic searches in the Cambridge Structural Database (CSD) in an attempt to select the most probable conformers.

d. Validate which conformers are indeed capable of interacting with the API molecule (giving preference to the compounds generally regarded as safe, GRAS).

e. Perform crystallization screenings by utilizing as many as possible crystallization [8].

Finally, the co crystals preparations generally occur by three traditional methods: slow solvent evaporation, liquid assistant grinding or solvent drop grinding. These co crystallization methods have been reported to be a useful, cost-effective and reliable for discovery and synthesis of new co crystals [9].

Solid State Characterization

There are a range of analytical techniques to characterize novel pharmaceutical solid forms. In general, these techniques should be used in combination to evaluate the structural features and the physicochemical properties of novel crystalline materials [10]. Among the most commonly used techniques we can mention the single-crystal and powder X-ray diffraction (SCXRD, PXRD) thermo gravimetric analysis (TGA), differential scanning calorimetric (DSC), hot-stage microscopy (HSM), infrared (IR) and Raman spectroscopy, solid state nuclear magnetic resonance (ssNMR) and scanning electron microscopy (SEM). After that complete characterization, solubility/dissolution studies and then bioavailability tests are carried out in order to predict the pharmacokinetic performance of the new API.

Impacts on Drug Bioavailability

The bioavailability of an API is the main prerequisite for the pharmacological action of a drug. Bioavailability is defined as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action" [11]. It is well consolidated that co crystals can improve both solubility and dissolution rate and consequently bioavailability of poorly soluble drugs. In the present review we will be quoting only reports where pharmacokinetic studies involving pharmaceutical co crystals have been performed which resulted in an enhance in the drug bioavailability.

Bioavailability of 6-mercaptopurine (ant metabolite agent), after the co crystallization of this API with is onicotinamide, was reported to remarkably improved by 168.7% as compared to the parent drug Chadha et al. [12] reported two co crystals of the ant diabetic drug glicazide with succinct and malic acids coformers. According to the pharmacodynamic and pharmacokinetic studies, the authors have evidenced a remarkable reduction in glucose level and higher Cmax in comparison to glicazide, respectively [13]. It was demonstrated that solubility and bioavailability of quercetin (flavonoid with antioxidant activity) can be potentially increased (more than 10 folds) by co crystals formation with caffeine, nicotinamide and the obrominecoformers [14].

According to Jung et al. [15] a pharmaceutical co crystal of the no steroidal anti-inflammatory drugindomethacin with saccharin showed a significant enhancement in the in vivo bioavailability of indomethacin [15]. Hicky et al. [16] demonstrated that the co crystallization of the antiepileptic agent carbamazepine with saccharin increase by several folds the drug plasma levels compared with a free base [16]. The co crystallization of the oral alkylation agenttemozolomide with succinic acid showed that the pharmacokinetic of the parent API as well as the co crystal is very similar, indicating that both solid forms are bioequivalent [17].

Conclusion

Crystal engineering and supramolecular chemistry have propitiated remarkable advances in the development of novel pharmaceutical co crystals and has been extensively used for this purpose. In last few years, these compounds have attracted considerable attention from the pharmaceutical community because they are a key to modulate biopharmaceutical properties (solubility, dissolution, bioavailability, etc.) of neutral or slightly ionizable APIs, and hence, offer the opportunity for fine-tuning of pharmaceutical formulations. In this mini review we have exemplified that the pharmacokinetic profile (with particular focus on bioavailability) of poorly water soluble drugs can be significantly improved trough co crystal formation.

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