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Editorial

Multicomponent Pharmaceutical Solids

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Multicomponent pharmaceutical solids is a hot topic that brings together the knowledge of crystal engineering and the need to achieve novel and effective drugs at lower costs for the pharmaceutical industry. Both the U.S. Food and Drug Administration and the European Medicines Agency encourage the use of pharmaceutical cocrystals for drug development, which is tightly regulated with appropriate guidelines. Indeed, in the past years, several cocrystal formulations have been approved and commercialized, for instance, Depakote® (2002), Suglat® (2014), Entresto® (2015), Steglatro® (2018), and Seglentis® (2021).

This issue collects 10 contributions. The first consists of a review article dealing with amorphous pharmaceutical solids [1]. Most of the multicomponent pharmaceutical solids reported are in crystalline form since they are thermodynamically more stable. Nonetheless, amorphous materials usually present higher solubility and a faster dissolution rate, hence being worth exploring due to improved oral bioavailability. In this context, Q. Shi, C. Zhang, et al. review the latest progress regarding the characterization of the physical stability of amorphous pharmaceutical solids.

The additional nine contributions are original research papers. First, C. Puigjaner et al. [2] compared the thermodynamic stability of three anhydrous polymorphs and thoroughly characterized three transient chloroform solvates of Bilastine, a second-generation antihistamine drug. Interestingly, the detailed structural study provides new insights into hydrate/solvate formation, paying special attention to the ability to build hydrogen bonding networks.

The physicochemical properties of pharmaceutical solids, such as solubility, thermal stability, and hygroscopicity, are highly dependent on their intimate solid-state structure. Hence, it is possible to modulate the pharmacokinetic profile of active pharmaceutical ingredients (APIs) by tailoring their crystal architecture. This is actually desirable for more than 80% of the drugs already on the market, which belong either to classes II or IV within the Biopharmaceutical Classification System (BSC), i.e., those exhibiting poor aqueous solubility. Indeed, the vast majority of the reported multicomponent pharmaceutical solids are devoted to enhancing the solubility of already-known APIs.

This is the case of the results reported by Y. Liu, G. Gan, et al., regarding the third-generation antipsychotic Aripiprazole [3]. The authors show new potential multicomponent formulations for this drug, highlighting the improved solubility of the corresponding salt with the coformer adipic acid. Single crystal X-ray diffraction and theoretical methods are employed to explore molecular interactions, while additional physicochemical properties are evaluated.

Fixed-dose formulations refer to multicomponent pharmaceutical solids in which all components are APIs. D. Choquesillo-Lazarte et al. [4] report the synthesis and characterization of furosemide/non-steroidal anti-inflammatory drug–drug pharmaceutical cocrystals, a combination of APIs that is quite frequent in clinics. Remarkably, the mechanochemical synthetic approach allowed for the avoidance of the formation of hydrates/solvates. Although solubility enhancement is not achieved in the novel cocrystals, improved thermal and thermodynamic stability profiles are given, opening the door to further research.

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Eutectic mixtures are frequently used in the pharmaceutical industry regarding research on drug delivery systems. B. Saikia et al. [5] explore the use of such eutectic mixtures to improve the solubility of the non-steroidal aromatase inhibitor aminoglutethimide, using three different non-isomorphous coformers: caffeine, nicotinamide, and ethenzamide. Solvent-assisted mechanochemical synthesis was also employed to obtain the novel binary eutectic mixtures, which were thoroughly characterized and proved to successfully enhance the solubility of the parent API.

In M. Benito et al.'s paper [6], efforts were made to rationalize the nature and strength of those supramolecular interactions present in six new multicomponent systems involving the modified nucleobase 9-ethyladenine and the coformer oxalic acid. Herein, salt screening was carried out by mechanochemical and solvent crystallization techniques, yielding two molar ratios and different anhydrous/solvated forms. Comprehensive computational analysis helps to fully understand the solid-state landscape, unveiling the relative importance of non-canonical hydrogen bonds.

Molecules included in the Generally Regarded As Safe (GRAS) list are used along with the drug precursor DL-mandelic acid to design novel multicomponent pharmaceutical solids in A. Castiñeiras et al.'s paper [7]. The authors focus their attention on the identification of recurrent supramolecular patterns thanks to detailed crystal structure and computational analyses. Solubility studies were also performed, which revealed an enhancement of the dissolution profile.

Drugs with a narrow therapeutic index, such as theophylline, are better administered with sustained-release formulations, which reduce the likelihood of adverse reactions. L. Marchiò et al. [8] address the optimization of theophylline pharmacokinetics by using the salification strategy. The authors successfully decreased the dissolution rate of the API, which might allow better control of drug release into the bloodstream, therefore reducing adverse effects without losing drug efficacy.

The salification approach can also be observed in the formulation of the anesthetic drug Lidocaine, which is found as the corresponding hydrochloride derivative in order to improve the solubility of the API. In C. Verdugo-Escamilla and A. Domínguez-Martín et al.'s paper [9], ionic cocrystals of lidocaine base and lidocaine hydrochloride are reported along with polyphenols as coformers. Interestingly, only those multicomponent solids involving lidocaine hydrochloride achieved improved stability thanks to a steric protection effect, in which chloride ions play a key role in promoting efficient packing, thus protecting the coformer from oxidation.

The last contribution of this Special Issue is devoted to multicomponent formulations of the non-steroidal anti-inflammatory drug Diclofenac, using nucleobases as coformers due to their versatility to build multiple H-bonding patterns [10]. Careful structure-property analysis reveals that the large surface exposure of two of the novel cocrystals favors their dissociation in aqueous media. The third species undergoes dissociation at a much lower rate, therefore allowing its solubility to be characterized with positive results.

In summary, the articles presented in this Special Issue represent some of the most recent research approaches to the study of multicomponent pharmaceutical solids. The vast majority of results are focused on crystalline solids. The combination of X-ray crystallography and computational methods provides a complementary and comprehensive view of the nature and strength of supramolecular synthons, which drive the crystal structure architecture and therefore the physicochemical properties of the novel multicomponent materials. Solubility and dissolution rate, as well as thermal and thermodynamic stability, are the most common properties assessed, in agreement with the limitations currently observed in the drugs already present in the pharmaceutical market. The latest advances in multicomponent pharmaceutical solids are devoted not only to obtaining API + GRAS-like coformer formulations but also API + API formulations, so-called fixed-dose formulations. Likewise, multicomponent pharmaceutical solids' research goes beyond cocrystals, and molecular salts, ionic cocrystals, cocrystal polymorphs, and even amorphous phases are currently being evaluated. There are still significant challenges to overcome. In this con-

text, further research on the development of structure-property studies is of paramount importance to the design of tailored properties and the future of multicomponent drugs.

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