JETI
Journal of Experimental and Tecnique Instrumentation
UFMS
Review

Crystal Engineering in the Design of New Solid Pharmaceutical Forms with Enhanced Pharmaceutical Properties

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DOI: https://doi.org/10.30609/jeti.v4i3.12950

Abstract. High-efficiency drugs and pharmaceutical formulations, produced in a sustainable way, and that present a favorable performance are widely required in public health. Among the pharmacokinetic properties of active pharmaceutical ingredients (APIs), the solubility is main variable since it regulate the availability in the biological target. Numerous formulations in the market and in the Brazilian National Health System (SUS) present serious drawbacks related to quality, manufacture and performance. In general, APIs are delivered in solid formulations and this characteristic represents a challenge for industry and academia since the therapeutic efficiency of an APIs is related to their crystalline structure, i.d structural multiplicity, polymorphism and composition. APIs may exist in different forms presenting different pharmacokinetic profiles. In addition, the characterization of the diversities of solid forms of an API, constitutes an innovative strategy to optimize pharmaceutical properties, providing opportunities for the creation of intellectual property and innovation for the country. In this work we will discuss several strategies related to the problem aiming to show the importance in the pharmaceutical area of solid state techniques like crystal engineering.

Keywords: mulcomponent solid forms, crystallography, crystal engineering, pharmaceuticals

1. Crystalline Solids and Pharmaceutical ingredients

Active Pharmaceutical Ingredients (APIs) - agents responsible for the pharmacological properties of a drug - are often administered in solid state as, for instance, in tablets, capsules, granules or draggers. Solid forms of oral use are the most widely used.[1-3] They are normally composed by one or more APIs as well as excipients. The molecules of the APIs are grouped into two large classes in the solid state. As the

tridimensional structure, the solid state can be classified into crystalline when they present a structural organization or amorphous otherwise. In the pharmaceutical sciences, the crystalline solid (crystals) is a convenient and practical way for the formulation process and storage APIs, since crystals are thermodynamically more stable than amorphous. This fact guarantees that, in the production and development of medicines, the API has a reproducible way of delivery taking the drug to the right place and at the right time. In this way, the solid-state properties of an API influence from the manufacture procedure until its absorption into the system (Figure 1).

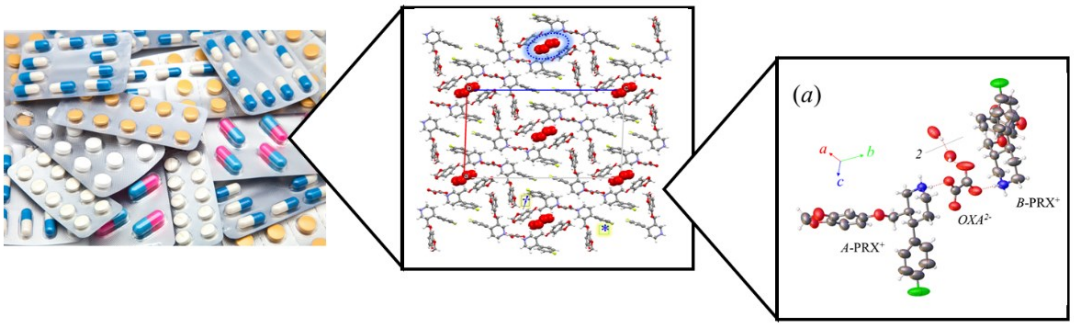

Figure 1. A medicine administered in the form of tablets consists of a pharmaceutical solid form whose main component is the API molecule. The identity of the solid (tridimensional crystal Structure) is strongly related with the physicochemical properties and performance of a drug.

As all crystalline solids, the APIs may be found in a large variety of different solid forms being able to aggregate into single component forms as well as in multicomponent ones. Over the past few decades, research aimed at developing solid modifications with specific properties has led to the design of different multicomponent systems which can be classified in different ways. Figure 2 shows one of these classification system. For amorphous solids, the same principles of classification are applied. Crystalline APIs may contain solvent molecules in the crystal structure, whose phases are now referred to solvates. The term hydrate is used for crystalline structures that contain water molecule(s) in their structure. On the other hand, the term salts is used for multicomponent solids resulting from the aggregation of different species by the formation of ionic units. Cocrystals, however, come from the aggregation of an API with other molecules (which may or not be also an API) in a single phase without the occurrence of charge transfers. In addition to these solid forms, it is still possible to form crystal lattices composed by ionic unit associates to neutral forms referred to salt-cocrystals or ionic cocrystals. It should also be considered that crystalline solids can exhibit polymorphic forms, containing the same chemical composition but presenting different internal structures, which arise from the

disparities in crystalline packaging resulting from the combination of different molecular conformations with the different possibilities of intermolecular interactions. Polymorphism is of fundamental importance in the pharmaceutical sciences. Bernstein *et al.* observed that at least 50% of APIs have at least some type of reported polymorphism.[4] A similar level of occurrence is also observed for salts, crystals, solvates and hydrates.

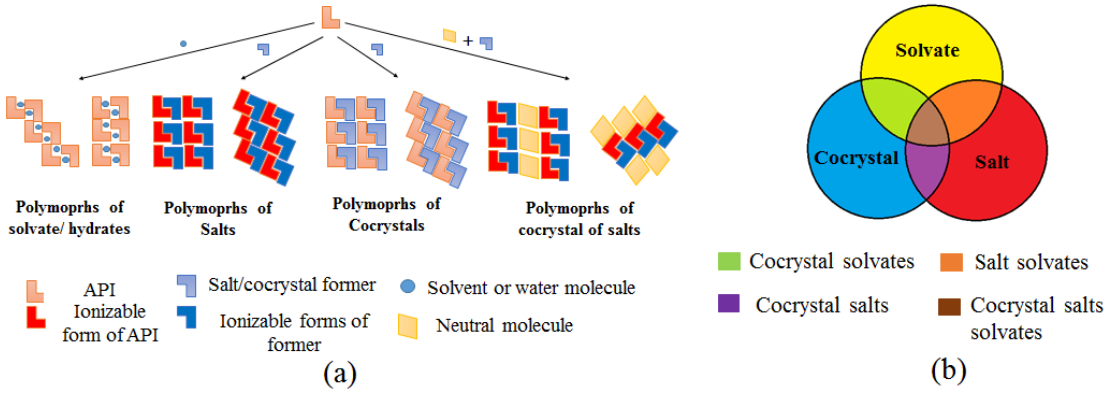

Figure 2 - Classification scheme of single and multicomponent solid forms of APIs (b) Vien Diagram of solid forms of APIs classification as Gelder *et al.*[5]

An API must have adequate physicochemical properties to ensure optimal pharmacokinetic performance. Unfortunately, some APIs, even with highly desirable pharmacological properties, can never reach their maximum potential because their physical and chemical properties in the solid state often end up strongly conditioning their bioavailability. Among the properties that determine the action of drugs and that strongly influence bioavailability we can mention the solubility. On the other hand, soluble and permeable compounds are able to cross membranes more easily and to be absorbed so that they can exert their therapeutic action. The Biopharmaceutical Classification System (BSC) provided by the U.S. Food and Drug Administration (FDA) is a guide for predicting drug absorption. In this system, APIs are classified into four classes according to their solubility and intestinal permeability. APIs limited by solubility are grouped into classes II and IV. It is worth remembering that in order to prepare this classification, the solid form of the API in question is specifically considered.

Different solid forms of the same pharmaceutical compound can have different chemical and physical properties. Thus, the development of new solid forms of an API has the potential to modify its dissolution, solubility and absorption. These variations are related to changes in its crystalline packaging due to the changes in the intermolecular interactions pattern. The coexistence of another component in the crystalline network alters

the system of intermolecular interactions, thus leading to modifications of the internal energy of interaction and, consequently, of enthalpy, which finally results in the occurrence of different physical-chemical properties. Often, the solubility of an API can be altered by using a more soluble multicomponent form, whether in the form of salts or cocrystals, for example. Historically, the formation of pharmaceutical salts is the main choice for overcoming solubility problems. APIs in the form of salts are usually more soluble than their neutral forms, so they are better absorbed. However, this technique is correlated to the existence of an ionizable group in the API molecule, which may not often be the case.

In addition to modifying aqueous solubility, differences in solid crystalline forms also affect thermodynamic parameters, such as fluidity, compression, compaction, density, hardness, stability, etc. The selection of an appropriate solid form of an API for its pharmaceutical formulation also influences industrial parameters such as the manufacturability, processing, storage and shelf life of a drug. It is desirable that the API be stable and does not suffer modifications during the manufacturing process, preserving its structure until its administration. Thus, unexpected solid-solid transformations during their processing may result in the failure of quality controls of the final product. As one of the main examples, we can mention the occurrence of unknown polymorphic phases in the manufacture processes that changed the way in which the pharmaceutical industry looks at the solid forms. The antiretroviral drug ritonavir exemplifies this case (Figure 3). This API had solubility problems due to the formation of a polymorphic form of unknown structure during the formulation of the drug.[4] Once the relationship between the different polymorphs was stablish, an effective way to solve the pharmaceutical problem was obtain but until that the product was taken off the shelves. The new formulation take its place more than a year later generating billions of dollars in losses.

Similarly, the exposure of the pharmaceutical product to high humidity during its storage could lead to the transformation of APIs in their hydrated phases.[6] For example, Carbamazepine, a drug widely used in the treatment of certain types of seizures and epilepsies, has two solid forms, one stable and one metastable (Figure 3). The latter can suffer a solid-solid phase transformation to its dihydrated phase when exposed to water vapor at temperatures above 37ºC.[7-8] For these reasons, the knowledge of the melting point as well as the dehydration temperature (for hydrates) of a phase is an invaluable tool in

determining its physical stability for a given manufacturing route, as many processes, such as grinding and compaction, could lead to an increase in the temperature of the API. Thus, hygroscopicity and hydration/dehydration processes are properties that could be successfully controlled and even modulated by changing the solid form of the pharmaceutical ingredient to be used in the final formulation. Given this context, in the last decades, regulatory agencies have intensified the characterization and the standardization in the production of pharmaceutical solids.

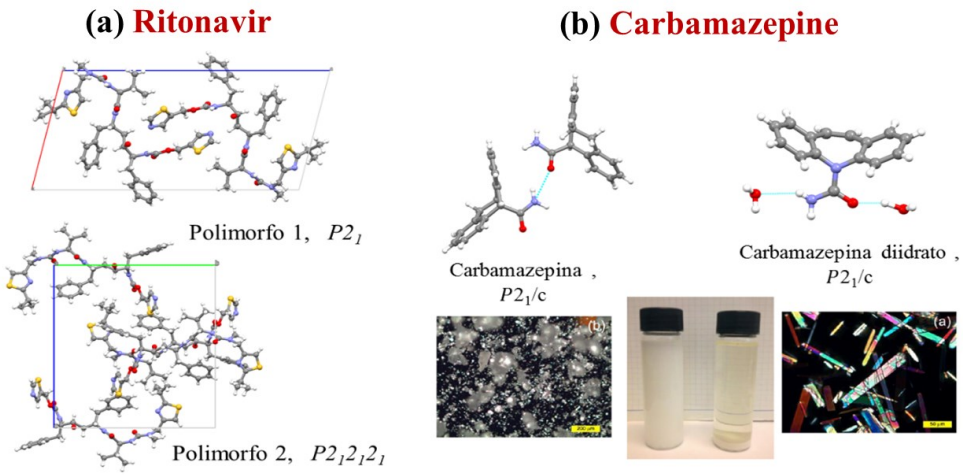

Figure 3: (a) Polymorphic forms of ritonavir involved in the API manufacturing process. (b) Occurrence of the dihydrated form of carbamazepine in API dispersions.

Considering the structure/property relationship established by the variability of solid APIs, the development of appropriate techniques for the correct selection of the form to be used in the formulation has been strongly consolidated in the pharmaceutical industry. There are a significant number of cases that demonstrate that the identification and characterization of solid multicomponent or polymorphic forms of APIs in the early stages of drug development is an interesting and attractive opportunity for the improvement of the formulations as well as the best path to avoid intellectual property. Problems. As examples, we can cite a work involving the synthesis of salts and crystals of the antifungal miconazole.[9] The maleate and nitrate salts and the fumaric and succinic acids cocrystals showed a significant increase in the solubility and in the percentage of drug dissolved in the intrinsic dissolution tests in relation to the free base. Another example reported in the literature involve the anti-diabetic gliclazide. Chadha[10] and collaborators showed that the maximum plasma concentration (C_{max}) of two co-crystals of

this API with succinic and malic acids, was increased about 1.5 times in comparison with the C_{max} of Gliclazide. In this context, the selection of an appropriate multicomponent form provides the opportunity to modify its pharmacokinetic and pharmaceutical characteristics.

Even when the variation of physicochemical properties in different solid forms is well known, it is not possible to predict a priori which properties could be modified or how they could be modified. We thus have that the number of crystalline modifications depends on structural and kinetic factors as well as "*on the time and the financial investment in the search for these new crystalline arrangements*".[2,4,8] The process of selecting an appropriate solid form of APIs is not a trivial exercise, as numerous different solid forms are possible for a given API. In fact, understanding, controlling and optimizing the main factors in the formation of multicomponent forms is a fundamental task and often difficult one to achieve. In the search for optimal solid forms of APIs, a scientific approach is to alter and control solid state properties without changing the pharmacophoric unit using, for example, the Crystal Engineering (CE) methods.

CE is used in this perspective for the generation of new multicomponent forms based on the principles of supramolecular chemistry and molecular recognition. It is one of the main areas of contemporary solid-state chemistry and results from an intimate relationship between supramolecular chemistry and crystallography. The investigation of the diversity of solid forms via CE has been shown to be innovative in both basic research and industry.[4] Therefore, the knowledge of which characteristics of an API to optimize, using the CE strategy, is of great use for the pharmaceutical industry. This scenario has provided opportunities for the development of new drugs and for the optimization of pharmaceutical formulations, since each solid form of an API can exhibit unique physico-chemical properties, therefore being considered as New Chemical Entities (NECs) and, as such, candidates for new drugs.

The pharmaceutical industry is currently experiencing a continuing crisis due to rising R&D costs, a decline in the number of products marketed and expiration of blockbuster drug patents (those whose sales provide annual revenues of more than Us$ 1 billion in the global market). Drug research and development is a long, expensive and arduous process, which is generally associated with a high risk and low success rate. Less than 1% APIs are successfully developed and appear on the market. Difficulties in the development of new pharmaceutical products have stimulated research in the field of

multicomponent pharmaceutical solids, since these can be designed beforehand and can be developed to have the desired properties such as better solubility, greater stability and in some cases even better pharmacological performance. Since the properties of the materials dependent on their solid-state structure, it is evident that solid-state modifications can be designed to decrease and even suppress the undesirable pharmacokinetic and pharmacodynamic properties of the APIs.

From an economic perspective, the research on multicomponent phases contributes to the lowering the production cost of APIs, since new patents with reduced production prices can be generated. As each form is unique, and its design and development are not usually "*obvious*", they characterize a technological innovation, so they can be protected and, as such, they may have its own patentable intellectual property. The emergence of new forms of APIs contributes to the expansion of intellectual properties with new patents of modified forms. The identification of new phases of APIs with promising improved properties, may led to the rapid development of a large number of candidates and possible formulations - ensuring that the time from the discovery of patentable NCE until its exit to the market may be much shorter since they can be prove to be bioequivalent to the reference API. In this way, the first phases of clinical trials do not need to be repeated, thus greatly reducing development costs and greatly shortening the time to market.

This context is of primary importance for drugs listed in classes II and IV of the Biopharmaceutical Classification System (BCS) that are already on the market and have limited action due its low solubility. Especially for those used to treat prevalent diseases in Brazil such as depression, systemic arterial hypertension, diabetes and infections in general. These diseases are of great relevance, incidence and have a huge social impact. [11] According to the World Health Organization, these constitute challenges for public health[12] due to aspects inherent to treatment and diagnoses. These are the main prospective causes of disability in the world over the next 30 years[12-13]. As they are diseases that require long and continuous treatment, it is important to develop safer, more efficient and cheaper drugs. For APIs in these classes, finding an ideal solid form is important. Additionally, this area of research supports the development of new technologies for the discovery of new APIs and the expansion of intellectual property (new patents). The search for new crystalline forms, as well as the characterization and standardization of new analytical

methods for the analysis/control of the drug production line are challenges for the pharmaceutical industry.

2. Conclusions and perspectives

Drug innovation strategies, aiming to increase efficiency and to reduce production costs, constitute an important demand from the Brazilian National Health System (SUS). The production of medicines, from their formulation to their commercialization, presents important costs that can be reduced using CE techniques. In addition, numerous formulations available on the market and in the SUS have drawbacks related to quality control, manufacturing problems and difficulties in product performance that can also be address using CE techniques. In a social context, innovation in this area consists of the generation/production of new pharmaceutical products effective in combating a disease, which may led to reduction in production costs and get improvement to health of the society. Medicines represent the main pathological assistance interventions. Given the rising costs of discovering new drugs, it is clear that investment and efforts in innovative strategies can be focused on studies of new pharmaceutical formulations of already known APIs. There are several strategies to achieve that goal, however, Crystal Engineering (EC) has emerged as a cost-effective very promising process for APIs optimization. CE have as a main objective the search for functional products with optimized properties, the so call Taylor-Made materials. It can also be associated to the Green Chemistry principles through the application of mechanochemistry process, thus reducing the environmental impacts of the exhausting drug discovery process. This area of research is in the interface of supramolecular chemistry and crystallography. It represent an important technical-scientific issue for Brazil, since its products may be transform in NCEs that could be plausible to be patented. Unfortunately, Brazil does not have neither the time nor money necessary to develop new drugs from scratch. We need medicines now and at reasonable costs. Is at this point that CE applied to pharmaceutical solids will be of great importance in the coming years as it has been already for several years in others developing countries like India and China. Those countries are today much better prepared to face these pandemic times that we are going through. This innovation represents the possibility to obtain incremental patents as well as other registrations. Such aspects are vital for public health since innovation can provide value-added drugs at more reasonable costs.

Acknowledgments

This study was funded by the National Council of Scientific and Technological Development - CNPq (Proc. #305190/2017-2 and #427308/2018-6) as well as the São Paulo Research Foundation, FAPESP (Proc. #2017/15850-0 and #2021/02522-0).

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