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Review

Chemometrics-assisted solid-state characterization of pharmaceutically relevant materials. Polymorphic substances

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ABSTRACT

Current regulations command to properly characterize pharmaceutically relevant solid systems. Chemometrics comprise a range of valuable tools, suitable to process large amounts of data and extract valuable information hidden in their structure. This review aims to detail the results of the fruitful association between analytical techniques and chemometrics methods, focusing on those which help to gain insight into the characteristics of drug polymorphism as an important aspect of the solid state of bulk drugs and drug products.

Hence, the combination of Raman, terahertz, mid- and near- infrared spectroscopies, as well as instrumental signals resulting from X-ray powder diffraction, ^{13}C solid state nuclear magnetic resonance spectroscopy and thermal methods with quali-and quantitative chemometrics methodologies are examined.

The main issues reviewed, concerning pharmaceutical drug polymorphism, include the use of chemometrics-based approaches to perform polymorph classification and assignment of polymorphic identity, as well as the determination of given polymorphs in simple mixtures and complex systems. Aspects such as the solvation/desolvation of solids, phase transformation, crystallinity and the recrystallization from the amorphous state are also discussed. A brief perspective of the field for the next future is provided, based on the developments of the last decade and the current state of the art of analytical instrumentation and chemometrics methodologies.

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1. Introduction

In recent times, a number of different issues regarding the solid state of active pharmaceutical ingredients (APIs) and their dosage forms, have evolved within the pharmaceutical industry and the academia, from mere scientific curiosities and subtleties to subjects that must be seriously and deeply addressed for every solid dosage form for practical, but mainly for regulatory reasons [1].

The characterization of pharmaceutical solids poses different problems than the characterization of the same materials in solution. The two main basic issues with pharmaceutical solids arise from the fact that the material is heterogeneous and the need to differentiate among highly similar coexisting compound signatures. Further, many properties are unique to the solid state, vanishing in solution. Here, the information provided by the analytical means, despite often being more detailed and complex than in solution, is usually insufficient to fully answer the analytical question. For these reasons, the study of materials in the solid state commonly demands a more complex combination of analytical techniques.

Solids of pharmaceutical interest can be pure substances or formulations. The main issues that need to be addressed in the comprehensive characterization of pharmaceutical solids include, but are not limited to, particle size and morphology, solid form identification, quantitation of mixtures of forms, selective detection of one or more forms in the presence of the others and conversion between forms. The same issues need to be studied in formulations, which also require to include the investigation of the influence of excipients. However, the complex nature of the latter anticipates that analysis of individual chemical species in dosage forms may be significantly more difficult.

Not less important, the choice of the analytical technique or set of techniques to use depends upon the nature of the analytical problem, the sample and the degree of data analysis required for interpretation. In addition, sampling and the extent of sample preparation, as well as particle size and shape must be considered.

1.1. Pharmaceutical polymorphism

Crystalline materials exhibit structural units which are regularly repeated to form a well-defined lattice. Pharmaceutical solids can exist in multiple crystalline solid forms, resulting from two or more different structural orientations (lattice structures and/or molecular conformations), each one with its own physical characteristics, without undergoing any change in their chemical composition. This well-known and recognized behavior is known as structural or crystal polymorphism and is usually mentioned in the specific literature as “polymorphism” [2].

Solvent molecules can also be incorporated stoichiometrically or non-stoichiometrically into the crystal structure, giving rise to various forms of crystals (solvates), a phenomenon termed solvatomorphism. Most often, the solvent included in the crystal lattice is water, so the term hydrate is more appropriate to designate these solids. Both, solvates and hydrates are to be considered pseudopolymorphs, and not true polymorphs [3]. Hydrates differ in their physicochemical properties from their anhydrous congeners, and these may have impact on therapeutic, manufacturing, commercial and even legal aspects of pharmaceutical development.

Unlike crystalline compounds, which exhibit orientational and positional long-range order in all three dimensions of space, there are solids which lack long-range order of molecular packing; these solids are termed amorphous. However, they may still have short-range order present over several molecular dimensions (microcrystalline amorphous) [4]. The battery of analytical techniques currently available for the quantification of amorphous and crystalline phases in pharmaceutical solids has already been reviewed elsewhere [5].

The polymorphs display individual physical properties, such as solubility [6] density, melting point, hardness, and crystal morphology (size, form, color), as well as specific chemical and physical stability and processability (powder flow, compressibility, hygroscopicity, etc.), which may impact in their drug product manufacture. Crystal polymorphism may also impact on the pharmaceutical properties of the drug product, including bioavailability, efficacy, biological activity, side effects, degradation, toxicity, etc., potentially affecting its quality and performance [7].

Achieving proper understanding of the polymorphic phases of a drug remains an important consideration in the development of pharmaceutical compounds, as it enables their better control. Lack of control over the polymorphic form may result in processes that yield solids with scarcely reproducible bulk properties, poor dissolution performance, as well as improper appearance, physical stability, or chemical stability [8–11].

A consequence of these differences is that for biological, manufacturing and stability reasons, for approval purposes regulatory bodies are currently focusing not only on chemical and microbiological aspects, but also on the solid-state characterization of the pure drug substances, as well as on their properties after being incorporated into the drug products. In addition, intellectual property and patenting rights can be claimed on pharmaceutical distinct forms; this turns imperative the most accurate analysis of the solid-state structures of the APIs.

Production of the wrong or unwanted polymorph during the manufacturing process of the API or the pharmaceutical drug product, or the presence of polymorphic mixtures may result in a faulty API, which will not possess the desired processing characteristics, or in a drug product that most likely will not satisfy the intended purpose. Therefore, despite the most recognized pharmacopoeias are still not paying due attention to the phenomenon of polymorphism, except in some specific cases, the proper identification of the polymorphic form of an API is currently a requirement along the pharmaceutical industry. Analogously, the determination of the abundance of a specific polymorph in polymorphic mixtures and in complex preparations such as drug products are relevant problems of modern day pharmaceuticals. No less important, polymorphic conversion, desolvation, amorphization and crystallization are also attracting great attention, because understanding these phenomena may help to prevent undesirable outcomes during processing and storage of both, APIs and drug products.

At the industry level, the unexpected occurrence of a polymorphic transformation may result in serious pharmaceutical issues, ultimately causing development delays, manufacturing pauses or cancellation of commercialization [12]. Therefore, current regulations require pharmaceutical companies to investigate and control polymorphism of drug substances to ensure product quality, safety and performance [13].

Hence, it is imperative to carry out in depth studies of the phenomenon and to establish suitable analytical methods and criteria to ensure the presence of the appropriate or acceptable solid-state

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