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Review article

Solid form screening – A review

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ABSTRACT

Solid form screening, the activity of generating and analysing different solid forms of an active pharmaceutical ingredient (API), has become an essential part of drug development. The multi-step screening process needs to be designed, performed and evaluated carefully, since the decisions made based on the screening may have consequences on the whole lifecycle of a pharmaceutical product. The selection of the form for development is made after solid form screening. The selection criteria include not only pharmaceutically relevant properties, such as therapeutic efficacy and processing characteristics, but also intellectual property (IP) issues. In this paper, basic principles of solid form screening are reviewed, including the methods used in experimental screening (generation, characterisation and analysis of solid forms, data mining tools, and high-throughput screening technologies) as well as basics of computational methods. Differences between solid form screening strategies of branded and generic pharmaceutical manufacturers are also discussed.

1. Introduction and background

In a classic paper by Haleblian and McCrone, polymorphism was defined as the ability of any compound to crystallise as more than one distinct crystal species [1]. However, in physical pharmacy the word 'polymorphism' is nowadays often used to cover a variety of solid forms of active pharmaceutical ingredients (APIs) and excipients including crystalline, amorphous, and also solvate/hydrate forms. Accordingly, the activity of generating, isolating and analysing different solid forms of an API is known as polymorph screening. In this paper, to avoid term confusion, all above-mentioned solid modifications are referred to as solid forms. The aim is to give a pharmaceutical outlook on solid form screening – what it consists of and what is the significance of it for the pharmaceutical field. As such, focus is not put on the screening and selection of salts and co-crystals.

1.1. Solid form screening

Nowadays solid form screening is a standard procedure in drug development, but it was not until the last decades of the 20th century that the whole pharmaceutical industry became aware of polymorphism even though the phenomenon had been known since the early 19th century [2]. The patent cases [3] and enormously expensive Hatch–Waxman agreements between branded and generic drug manufacturers [4], and production problems such as the sudden appearance of another form of ritonavir (with low solubility and bioavailability) [5] were needed for the industry to start taking polymorphism seriously. Regardless of the fact that solid form screening is a regulatory requirement for new pharmaceuticals [6], the whole topic remains still somewhat open since no universal guidelines on solid form screening can be written because every compound possesses unique properties. Further, all polymorphism-related phenomena, e.g., nucleation, are not yet fully understood [7,8].

The aim of solid form screening is to find the optimal form with the best characteristics for development. In order to be able to select the optimal form, knowledge of as many as possible forms is needed. The choice of the form for development is usually a compromise between physical, chemical, pharmaceutical and biopharmaceutical properties (see Section 1.2). Traditionally, the most stable form is favoured over other forms because of its lower tendency to solid phase transformations. It is important to identify the stable form as early as possible in the drug development process to avoid subsequent setbacks [9,10]. However, metastable forms are sometimes deliberately chosen – usually for better solubility and thus bioavailability [11]. Solid form screening should not be a one-time effort performed only during the preformulation stage

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of drug development. Instead, the solid state of the API should be monitored in a continuous fashion also during scale-up and manufacturing, to detect the occasional event of late appearing polymorphs as early as possible.

Solid form screening can be approached experimentally and computationally. Experimental screening consists of the preparation step, during which various forms are generated and isolated (see Section 2.1), and the analysis step, which involves the use of various measurement techniques (see Section 2.2) and also the data analysis (see Section 2.3). Computational methods of polymorph prediction (see Section 3) have evolved markedly during the last years, but one cannot fully rely on them yet. Even if the crystal structures are not predictable, computational methods can be used to help rationalise the experimental procedures [12] and decide whether the stable form has been found or not [13]. Solid form screening is one of the cornerstones of drug development and plays an important part in pharmaceutical product lifecycle management [14]. If most of the relevant forms are found the innovator company can achieve a very valuable intellectual property (IP) situation. Poorly conducted screens and unsuccessful patenting strategies on the other hand open new possibilities for competitors (see Section 4).

1.2. Differences between solid forms and their implications on physical, chemical, pharmaceutical and biopharmaceutical properties

In the crystalline state (polymorphs, solvates/hydrates, co-crystals), the constituent molecules are arranged into a fixed repeating array built of unit cells, which is known as lattice, whereas in the amorphous state there is no definite long-range order [15,16]. Polymorphs contain molecules of only one chemical species in their unit cells. There are two ways in which crystal lattices can form: packing polymorphism and conformational polymorphism. If rigid molecules with a specific conformation are packed in different arrangements, then it is referred to as packing polymorphism, whereas conformational polymorphism denotes crystal forms that consist of flexible molecules with different conformations packed in different arrangements [16]. See paracetamol [17] and L-glutamic acid [18] for examples of packing and conformational polymorphism, respectively.

In case the unit cell is built of host molecules (the API) accompanied by guest molecules the resulting solid form is called a solvate or a co-crystal depending on whether the guest species is liquid or solid at ambient conditions, respectively [19]. If the guest molecule is water then the term hydrate is used. (There has been, and still is, controversy in the literature regarding the nomenclature of multi-component crystals.) Solvates and co-crystals can also exhibit polymorphism. Hydrates are the most common solvates and deserve special attention. Many APIs are capable of forming hydrates due to the small size and multidirectional hydrogen bonding capability of the water molecule [20,21]. Hydrate formation stabilises the crystal structure via intermolecular bonding in the crystal lattice, resulting in hydrates being the stable forms in aqueous surroundings (below dehydration temperature). Many hydrates are also stable in ambient conditions, and therefore are quite often chosen as the form for development. The hydrate form can be chosen for development to avoid hydrate formation during downstream processing, but then again with hydrates there is a risk of dehydration. A classification system of hydrates has been suggested [22].

Amorphous state can be the result of either physical manipulation or the intrinsic nature of the compound [23]. The amorphous form is the most soluble form, but on the other hand, it is also the form with the lowest stability. The current trend of new APIs getting less and less soluble has given rise to the use of metastable forms in formulations and also another research topic, stabilisation of metastable forms and formulations thereof [18,24,25]. The physical stability issues are the main hurdles in developing formulations of amorphous APIs [26]. Regardless of being stable in "dry" conditions over the whole shelf-life, metastable forms may rapidly convert to the stable form upon administration, since solvent-mediated solid phase transformation kinetics are faster than those of solid-solid transformations. Therefore, the solubility advantage of amorphous (and other metastable) forms may not always be fully exploited [27].

Table 1
Physical properties that differ among various solid forms

Packing properties	Unit cell volume (crystalline forms only), density, refractive index, hygroscopicity
Thermodynamic properties	Melting point, enthalpy, entropy, free energy, solubility
Spectroscopic properties	Electronic transitions (UV–vis spectra), vibrational transitions (IR and Raman spectra), rotational transitions (far-IR or microwave spectra), nuclear spin transitions (NMR spectra)
Kinetic properties	Dissolution rate, rates of solid-state reactions, stability
Surface properties	Surface free energy, interfacial tensions, crystal habit
Mechanical properties	Hardness, tensile strength, compactibility, tableting, flowability

Modified from [16].

The solid forms of a given API can have significantly different physicochemical properties that can affect its performance [1,28]. Some of these properties are listed in Table 1. If solubility and/or dissolution rate are dependent on the solid form, the bioavailability of the API can be affected. This is a particularly important note when developing BCS class II APIs (low solubility and high permeability) with dissolution dependent bioavailability [29]. Examples of APIs with bioavailability problems due to solid-state phenomena are carbamazepine [30,31] and ritonavir [5]. Mechanical property differences can affect processing behaviour, and this is the case, for example, with paracetamol [32]: direct compression of form II is feasible, whereas with form I, binder excipients have to be used [33]. Also different forms of theophylline [34] and sulfamerazine [35] have been reported to show different processing characteristics. Stability is a very important property of a solid form, considering that raw materials and pharmaceutical products may be stored for prolonged periods and the solid state must remain unchanged. In addition to physical stability, chemical stability also has to be taken into account. Chemical reactivity can vary between different solid forms, and sometimes certain solid forms can be used to cause reactions when desired or to prevent reactions when they are to be avoided [36]. For examples of differences in chemical stability between forms see prednisolone *tert*-butylacetate [37] and quinapril HCl [38].

2. Experimental solid form screening

2.1. Generation of solid forms

2.1.1. Basics – thermodynamics and kinetic effects

Crystallisation is the key experimental technique used to execute solid form screens. Within this review, crystallisation is considered as a tool to generate multiple solid forms of a pharmaceutical compound; the fundamental theoretical aspects of this process can be found elsewhere [39,40]. Classically, the crystallisation process is described in terms of two distinct steps, nucleation and crystal growth [41], with the resulting physical form being the consequence of the kinetic relationship between these two elementary processes. In other words, for a polymorphic system the polymorph that nucleates first is thought to come from the cluster that exhibits the fastest nucleation rate as a result of its lowest free energy barrier (ΔG) to nucleation. However, the nature