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Density fluctuations in amorphous pharmaceutical solids. Can SAXS help to predict stability?

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This paper is dedicated to Professor Piero Baglioni, on the occasion of his 65th birthday.

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ABSTRACT

The analytical potential of X-ray small-angle scattering (SAXS) combined with simultaneous wide-angle diffraction (WAXS) has been explored on the example of three active pharmaceutical ingredients, (desvenlofaxine, simvastatin, and sulfamerazine, resp.) with the aim of identifying quantitative parameters obtained from SAXS that allow to describe the nano-structural characteristics of different amorphous forms and to monitor the processes of amorphisation and ageing. Cryo-milling, co-milling with polymer, melting and melt-quenching have been used for amorphisation of initially crystalline powders. In parallel to SAXS, the WAXS patterns have been obtained to fingerprint the crystalline state. The SAXS results demonstrate strong, systematic nanostructure variations in amorphous samples obtained by different milling conditions, or by melt-quenching. It has been found that the mean-square density fluctuation, directly obtained from the SAXS invariant, is a sensitive and robust parameter to characterize the degree of nano-heterogeneity, which is related to entropy and hence thermodynamic stability. The SAXS curves also allow estimates of amorphous domain sizes of different density. The propensity to recrystallize or to remain amorphous, respectively, upon ageing has been found to depend on the existence of domains in the starting amorphous materials.

1. Introduction

In pharmaceutical technology, amorphous formulations have been receiving strong growing interest over the past decades [1–4]. On the one hand, this is due to their special properties, e.g. dissolution and bioavailability differing from crystalline forms, and on the other hand to patent and/or regulatory aspects, since most conventional formulations are based on crystalline forms. In contrast, amorphous phases are frequently generated unintentionally during manufacturing of drug substances (crystallization, drying milling, sieving etc.) and/or drug product (granulation, compaction, coating etc.) [5]. Such unintended solid-state disorders are often the origin for physical instability (caking, agglomeration etc.) as well as chemical instability of pharmaceutical products. On the other hand, many pharmaceutical excipients include diverse amorphous polymers. Structural characterization of amorphous states of large molecules, biologics such as proteins or peptides, is likewise crucial for emerging therapeutics. Therefore, amorphous state characterization is one of the critical steps in rational pharmaceutical product development with optimized physical and chemical properties.

The common conception of the term 'amorphous' refers to a material without characteristic shape or form such as gasses, liquids or glasses. In material science and condensed matter physics 'amorphous' is considered as a material that does not show discrete Bragg peaks in X-ray diffraction. The question arises, whether the amorphous state of a solid material consists of fully random arrangements of molecules forming a continuum of constant density, or rather contains supramolecular domains, which constitute density fluctuations with more or less pronounced boundaries [6–10].

Abbreviations: SAXS, small-angle X-ray scattering; WAXS, wide-angle X-ray scattering; SWAXS, small-and wide-angle X-ray scattering; XRPD, X-ray powder diffraction.

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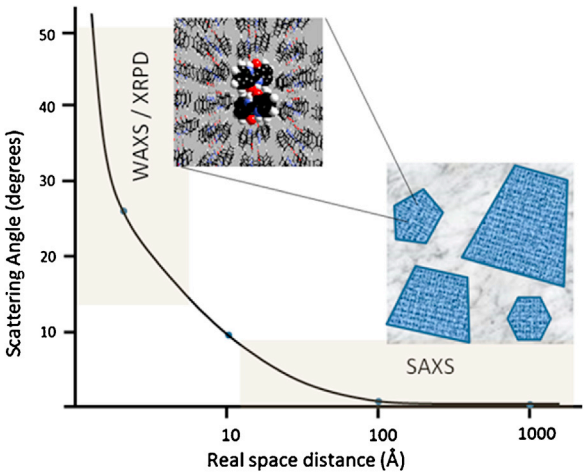

Fig. 1. Sketch of the different spatial and angular widows of SAXS and WAXS.

The understanding of structure in amorphous states is still far from satisfactory. The reason for this is, that X-ray powder diffraction (XRPD), as the standard X-ray method in solid state structure analytics [11,12], is generally limited to small molecular dimensions, about 1–10 Å, while the above-mentioned density fluctuations arising from supramolecular assemblies are likely to be much larger. X-ray small-angle scattering (SAXS) [13,14] which covers the size range of typically 1–100 nm (10–1000 Å), has so far found comparatively less use in pharmaceutical structure analytics despite its high potential in nanostructure analytics. The optimal method is clearly a combination of the two, i.e. combined small- and wide-angle scattering [15], in one experiment as schematically shown in Fig. 1.

Various other techniques are being used in combination to analyse the amorphous solid state produced from a crystalline state at compositions relevant to pharmaceutical intermediates and/or finished products. Among others, this includes calorimetric analysis [16] and spectroscopic techniques, such as, terahertz [17] Raman [18] and magnetic resonance spectroscopy [19]. In trying to quantify the degree of amorphisation, macroscopic blends of amorphous and crystalline material at varying ratios are often used for calibration. This is questionable, however, since it does not represent the situation in real amorphous/crystalline systems, where ordered and disordered domains coexist at a continuum of length scales, extending down to the meso- and nanoscopic range. Considering this fact, the frequently quoted 'percentage of amorphicity/crystallinity' does not represent the structural fluctuations at the meso- and nanoscale, which appear to be the important factors for pharmaceutical performance and stability. These fluctuations are the domain of SAXS.

1.1. Brief summary of the SWAXS technique

SAXS is observed wherever a material contains density fluctuations (static or dynamic) with domain sizes of d > 10 Å (1 nm). In 'scattering space', which is related to real space by Bragg's law $2.\sin\theta = \lambda/d$ (where 2θ. . .scattering angle, λ. . .X-ray wavelength, typically 1.54 Å for Cu-K_α radiation, and d. . .real-space distance), the angular region of interest for the d-range of 10–1000 Å is hence between zero and about 8°, requiring an angular resolution in the order of milli-radians is (1 mrad = 0.056°). XRPD, for X-ray optical reasons, typically covers the range between about 10° and 90°. This is the reason for the special experimental design for SAXS instruments.

As mentioned before, in studies on crystalline-amorphous hetero-phase systems both aspects, the crystallographic structure (size scale <1 nm) within the crystallites or domains, as well as the nanostructure of the domains (size scale > 1 nm) are of interest. For this purpose, a combined instrument for simultaneous small-and wide-angle detection (SWAXS, Ref. [15]) has been designed, which was used in the present study (S3-MICRO, formerly Hecus X-ray Systems, Graz). This employs high-brilliance micro-point focusing optics, which facilitates direct measurement of undistorted SAXS patterns by high-resolution detectors.

Fig. 2 shows a typical example of a SWAXS result: the SAXS curve shows a strong diffuse signal at lowest angles corresponding to density fluctuations in the range of 1–100 nm, and the WAXS range shows essential parts of the high-resolution powder crystallographic pattern ('Bragg-peaks'). While the angular scale in the WAXS range is limited to 18–26° for technical reasons, this is sufficient to fingerprint the underlying crystal structure, as shown by the comparison to the classical XRPD pattern of the same compound. It is also noteworthy, that the WAXS patterns show much more detail than conventional XRPD.

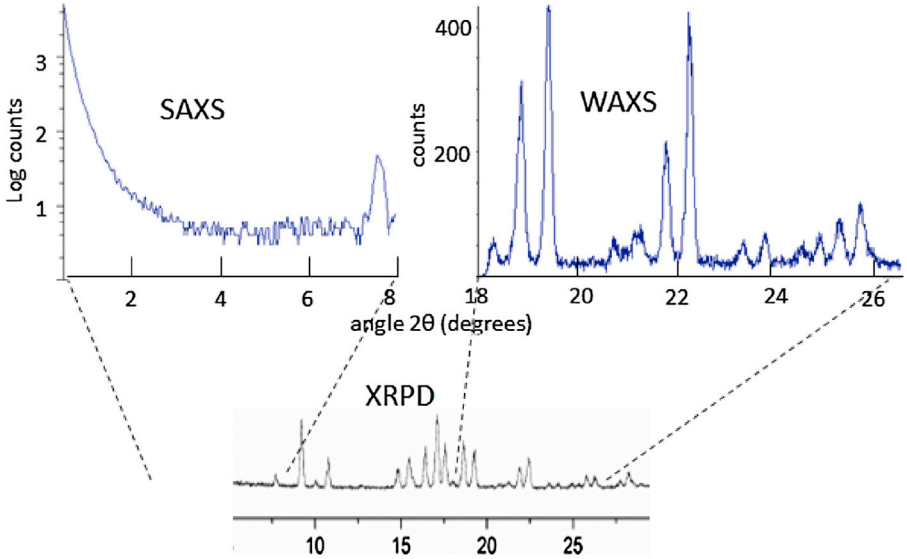

Fig. 2. SAXS, WAXS, and XRPD, respectively, of crystalline simvastatin powder. SAXS and WAXS patterns are obtained simultaneously. XRPD trace reproduced from Craye et al., Ref. [20].

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