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Benefits and Challenges

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Marzena Rams-Baron
Institute of Physics
University of Silesia
Chorzów, Poland

Renata Jachowicz
Chair of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy
Jagiellonian University - Medical College
Kraków, Poland

Elena Boldyreva
Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences
Novosibirsk State University
Novosibirsk, Russian Federation

Deliang Zhou
AbbVie
North Chicago, USA

Witold Jamroz
Chair of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy
Jagiellonian University - Medical College
Kraków, Poland

Marian Paluch
Institute of Physics
University of Silesia
Chorzów, Poland

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Contents

Chapter 1
Why Amorphous Drugs?

Low aqueous solubility of active pharmaceutical ingredients (APIs) is one of the most important challenges facing drug development researchers today [1, 2]. With the development of computational chemistry and high throughput screening methods it is possible to obtain a large number of compounds with attractive therapeutic activity. However, at the same time the selection of novel active molecules with suitable biopharmaceutical properties (like solubility, intestinal permeability) becomes a great challenge and a bottleneck in drug development. Statistically, more than 40% of approved drugs and even 70–90% of those under investigations are poorly water-soluble and additional efforts are required to improve their water solubility [3–5].

The rate of drug absorption depends on the complex interplay of various physicochemical and physiological conditions [6]. Among them Amidon et al. have distinguished membrane permeability and drug solubility/dissolution rate as those of fundamental importance for oral drug absorption [7]. In the framework of the biopharmaceutical classification of drug products, depending on their aqueous solubility and gastrointestinal permeability, these are divided into four groups distinct in terms of expected in vivo performance. The APIs with poor water solubility are classified as class II (with low solubility but high permeability) and class IV (with low solubility and low permeability). The currently observed trend in drug discovery indicates the rapid and continuous growth of class II compounds and the corresponding decrease of class I drugs which due to high solubility and high permeability are much easier to formulate [4].

The increasing amount of poorly water soluble chemical entities appearing during development research motivates pharmaceutical companies to search for novel solubilizing approaches able to overcome the urgent problem of their inefficient biopharmaceutical performance [3, 8–10]. In the case of drugs which can penetrate the intestinal mucosa easily, like class II drugs, the insufficient solubility will be a factor limiting their bioavailability. To trigger biological response the drug has to dissolve in biological fluids sufficiently enough to exert the desired therapeutic response. If the drug cannot be dissolved fast enough, it might pass the absorption

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site without appropriate action [11]. Increasing the dose may induce the desired outcome, however, it raises other problems relating to the proper patient compliance.

Although the nature of solubility and dissolution process are different, the former is a purely thermodynamic phenomenon while the latter is a kinetic event, they are closely related to each other. This relationship can be rationalized by modified Noyes-Whitney equation [12, 13]:

$$\frac{dC}{dt} = K(C_s - C_t) \tag{1.1}$$

where dC/dt is the dissolution rate, C_s is the drug solubility at saturated equilibrium condition and C_t denotes the concentration of drug dissolved at time t. The constant $K = AD/h$ depends on the diffusion coefficient D, value of surface area available for dissolution A and the thickness of diffusion layer h. Various physicochemical and structural factors may tune the parameters in Eq. (1.1). It is difficult to alter the diffusion coefficients of drug in biological fluids or thickness of diffusion layer since both quantities are governed by viscosity or hydrodynamics inside the gastrointestinal track [14]. Thus, one can deduce the following possibilities to enhance the dissolution profile of a drug, i.e. increasing the particle surface area and/or improving the drug saturated solubility in the gastrointestinal fluids. These solutions can be realized in a number of different ways giving raise to different formulating approaches which are summarized in Table 1.1. Each approach has its own advantages and weak points that need to be considered. Matching the

Table 1.1 Formulation approaches on the basis of BCS classification

BCS class	I	II	III	IV
Solubility	High	Low	High	Low
Permeability	High	High	Low	Low
Examples	Verapamil hydrochloride, warfarin sodium,	Diazepam, ibuprofen, glibenclamide, nevirapine, nifedipine, ritonavir	Cimetidine, amoxicillin, captopril, chloramphenicol	Dapsone, paracetamol, sulfamethoxazole
Formulation strategy	Capsule or tablet	*Physical modifications:* – particle size reduction – solid state modifications (polymorphs, co-crystals, amorphous forms) – complexation – solubilization by surfactants – drug dispersion in appropriate carrier *Chemical modifications:* – prodrag application – salt formation	Capsule or tablet, absorption enhancers	The same as for BCS II, absorption enhancers

Adopted from [5]. Examples taken from [15]

optimal formulation strategy to the drug development is a time and cost consuming task. To make a rational decision several factors need to be taken into account, for example, the physicochemical properties (e.g. pKa, log P, solubility, stability etc.) or the targeted profile of developing product (e.g. required dose, preferential administration route) [5].

Among the available approaches aimed at improving the dissolution behavior of poorly-water soluble drugs amorphization has been considered. Conversion of crystalline drugs into the amorphous form has been recognized as an effective way to achieve the longstanding goal of pharmaceutical science and drug developments, i.e. beneficial drug dissolution in vivo [16, 17]. It is possible due to the unique nature of the amorphous state (disordered nature and high energy) which differs substantially from the crystalline state. On the market a few examples of products containing amorphous API can be found, for instance Accolate® (zafirlukast), Ceftin® (cefuroxime axetil), and Accupril® (quinapril hydrochloride) [18].

The differences between crystalline and amorphous solids are schematically depicted in Fig. 1.1. When we cool a liquid slowly, allowing nucleation and crystal growth to occur, the drop of enthalpy and volume observed at the melting temperature (T_m) is due to the presence of a first order liquid-crystal transition. Contrary, when the liquid will be cooled fast enough to avoid crystallization, its liquid-like properties will be preserved below T_m in the supercooled liquid state. As we continue decreasing the temperature the liquid-glass transition will take place. The observed change in the slope of V(T) or H(T) determines the glass transition

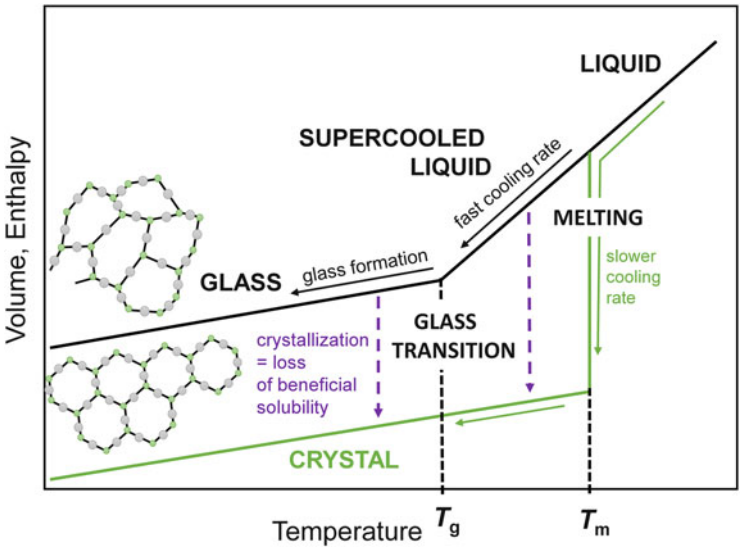

Fig. 1.1 Temperature dependence of volume and enthalpy at constant pressure. Fast cooling may lead to glass formation, while for slower cooling rates the crystallization may likely occur. Besides, crystallization may be observed from glassy or supercooled liquid states canceling any improvements in drug dissolution properties

temperature (T_g). Then, the material becomes an amorphous solid with macroscopic properties distinct from equilibrium values. It is worth mentioning that the cooling process is accompanied by a huge change in rheological properties. Below T_g in the glassy state the system is so viscous that its inhibited molecular mobility in relation to cooling rate is responsible for its fall out of equilibrium [19]. From a pharmaceutical perspective both glassy and supercooled liquid states are relevant. Usually, we keep the drugs at room temperature which corresponds to the glassy state of most pharmaceuticals. However, it is necessary to study amorphous drugs both below and above T_g since higher-temperature conditions corresponding to the supercooled liquid state may be applied during drug manufacturing. Due to higher molecular mobility the risk of drug conversion to crystalline form increases.

In general, the proper processing of crystalline material (e.g. by mechanical activation during milling, fast melt cooling, rapid precipitation from solution) [16] allows for material transformation into the amorphous form. Instead of three-dimensional ordering typical for crystalline lattice we obtain a structure with random atomic arrangement. Amorphous solids, in comparison to crystals, do not exhibit the long-range ordering (LRO). Instead, short range ordering (SRO) relevant only over few molecular dimensions can be found [19]. The faster dissolution and beneficial absorption of drugs in amorphous state is related to their higher free energy in comparison to crystals [3, 20]. The thermodynamics of solubilization is driven by the difference in the Gibbs free energy of initial state formed by undissolved components and final dissolved state. Since the amorphous state has higher free energy when compared to crystalline state less energy is necessary to dissolve when the amorphous form is applied. Thus, better dissolution rates should be expected. Attempts to estimate the actual solubility benefits arising from the application of drug in the amorphous form were made by Hancock and Parks [21]. Based on simple thermodynamic considerations they estimated that in the case of the amorphous forms 10- to 1600-fold improvement of drug water solubility in comparison to crystals should be expected. However, the measured values are usually significantly lower which was explained by difficulties in their experimental determination.

The excess thermodynamic properties of the amorphous state, like its greater entropy, enthalpy and free energy as well as its higher molecular mobility make the amorphous drugs more prone to crystallization. So far finding an effective stabilization approach is the major challenge related to the development of drugs in the amorphous form. The crystalline drug forms, more stable and easier to handle, dominate the pharmaceutical market for practical and economical reasons. However, the importance of the problem of insufficient APIs solubility encourages pharmaceutical companies to support and invest in new solutions, even those requiring additional efforts to obtain the beneficial drug absorption in vivo. Therefore, drug compositions based on amorphous active ingredients attract particular interest despite their unstable and problematic nature. The emphasis in developing amorphous formulations is put on searching drug compositions providing stability at each stage of drug processing—from its manufacturing to administration. The progress we are witnessing today, reflected in the growing number of amorphous

products available on the market is related to the successful implementation of amorphous solid dispersions technology. This concept, substantially improving water solubility and effectively protecting against drug recrystallization, allows for successfully entering of amorphous products onto the pharmaceutical market and secured their stable position in the offer of pharmaceutical companies.

Searching for stable amorphous drug formulations is a complex issue which cover a variety of challenges that we have to face at each stage of the drug product lifecycle. All should be predicted and resolved at the initial stage of research and drug development. Without complete understanding of the theoretical principles which are responsible for the recrystallization behavior, achieving the desired goal of producing efficient, well-soluble and safe amorphous drug product will be unattainable. It is well known that the process of drug discovery is extremely costly and highly risky. To save time and money unnecessarily lost during verification of ineffective solutions, a rational approach to the problem of amorphous drug instability is required. Such an approach requires interdisciplinary knowledge, skills and insights into the problems. The recrystallization of amorphous content might be promoted by elevated temperature, mechanical stress or humidity at each stage of drug processing, storage or even administration. The systematic investigations of crystallization behavior of amorphous drugs at different thermodynamic conditions and a comprehensive insight into manufacturing procedures allows one to establish processing conditions minimizing the risk of drug recrystallization. Only in-depth understanding of factors controlling crystallization kinetics allows for design of effective stabilizing solutions. The lack of such knowledge makes it impossible to understand the reasons of unexpected failure at a formulation stage.

A large number of reports concerning amorphous pharmaceuticals reflects the amount of work and efforts that have been made to advance this field in the last decades. This motivates us to summarize the current state of the art and indicate the paramount perspectives for future development. This book is addressed to people who are motivated to work with amorphous pharmaceuticals, but do not understand in detail what truly impacts their behavior. Our goal is to increase their awareness by improving understanding of the benefits and challenges associated with the application of high energy amorphous forms as active pharmaceutical ingredients. Based on our own experience, we refer to common problems that one may experience when starting work with amorphous drugs, but also we present here the robust solutions how these potential difficulties may be predicted and overcome. Practical and technological aspects are presented along with theoretical background allowing a rational approach to the task of amorphous drug preparation. Content of the book should guide those who are interested in amorphous formulations through the process of new product development decreasing the risk of failure. This book is not only dedicated to those who are actually involved in the implementation of amorphous formulations. Students and scientists who are simply interested in learning the subject, through many examples contained in the book, can understand the phenomenon of amorphous pharmaceuticals also. This book covers all key theoretical and practical issues related to working with pharmaceutical materials in the amorphous form. The particular chapters were prepared by experts from

different fields—physicists, pharmacists and representatives of pharmaceutical companies, which allows discussion of the problems from different perspectives.

To fully understand the properties of amorphous pharmaceuticals, one must have a thorough knowledge about theoretical concepts standing behind them. Thus, at the beginning the fundamental aspects concerning order-disorder transition and structure-property relationship for amorphous and crystalline phases will be outlined. In Chap. 2 by introducing the physics of disordered systems will provide a theoretical background for further considerations contained in the book. In Chap. 3 we focus on bioavailability advantage of amorphous formulations. A short review of the current state of the art methods of drug amorphization is provided in Chap. 4. Various manufacturing technologies are discussed there, from those applied in the laboratory environment to the most common approaches in the pharmaceutical industry like hot melt extrusion or spray drying. In Chap. 5 we will focus on the biggest challenge associated with amorphous drug application, i.e. their tendency for recrystallization. Understanding which factors are responsible for the recrystallization behavior is crucial to fully exploit and commercialize the potential of amorphous formulations in the future. The chapter will cover some fundamental aspects concerning the mechanism of nucleation and crystal growth, their resultant kinetics and methods of their experimental determination. From an industrial perspective finding drug properties that correlate with its recrystallization behavior is extremely important to facilitate the process of amorphous drug development. The experimental opportunities and existing models of drug long-term stability prediction are discussed extensively. Finally, we discuss the most long-standing issue in the field concerning methods of amorphous drug stabilization. Various well-established strategies and the most recent experimental results are presented and comprehensively discussed to give insight into the actual state of the art and to point out the most exciting research topics in the field. The last chapter gives some basic insight into various practical aspects of amorphous drug formulation and manufacturing (Chap. 6). To properly select the formulation composition and processing technology, the effect of different variables on quality and performance of the final product must be thoroughly understood. We hope that issues carefully chosen by us and described herein provide an in-depth understanding of the various aspects of working with amorphous products which will translate into further progress in this field. We believe that our expertise and interdisciplinary experience which we share with the readers will enable them to confidently and consciously enter the world of amorphous drug formulations in the future.

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Chapter 2
Order vs. Disorder in the Solid State

2.1 Perfect Order (Crystalline Materials)

2.1.1 Periodic Structures

According to the definition given by the International Union of Crystallography, "*by "crystal" is meant any solid having an essentially discrete diffraction diagram*" [1]. A typical diffraction pattern corresponding to a "classical" periodic, perfect crystal looks like the one shown in Fig. 2.1 [2]. This pattern corresponds to the inner structure of the material, which can be represented as an array of periodically repeating fragments. The whole structure can be described by defining the repeating fragment (basis) and a set of three non-coplanar unit vectors. The three unit vectors can be used to build a parallelepiped: a unit cell. Translations are not the only symmetry elements that can be used to describe a periodic structure. Combinations of mirror reflections, rotations, inversions, glides and screw rotations form groups, that are termed space symmetry groups [3]. A periodic structure can then be described only by defining the crystallographic[1] coordinates of an asymmetric unit and the symmetry operations of the space symmetry group.

2.1.2 Aperiodic Structures

For a periodic crystal structure the positions of the diffraction patterns can be expressed by:

[1]Crystallographic coordinates are defined in the coordination system related to the three primitive translation vectors.

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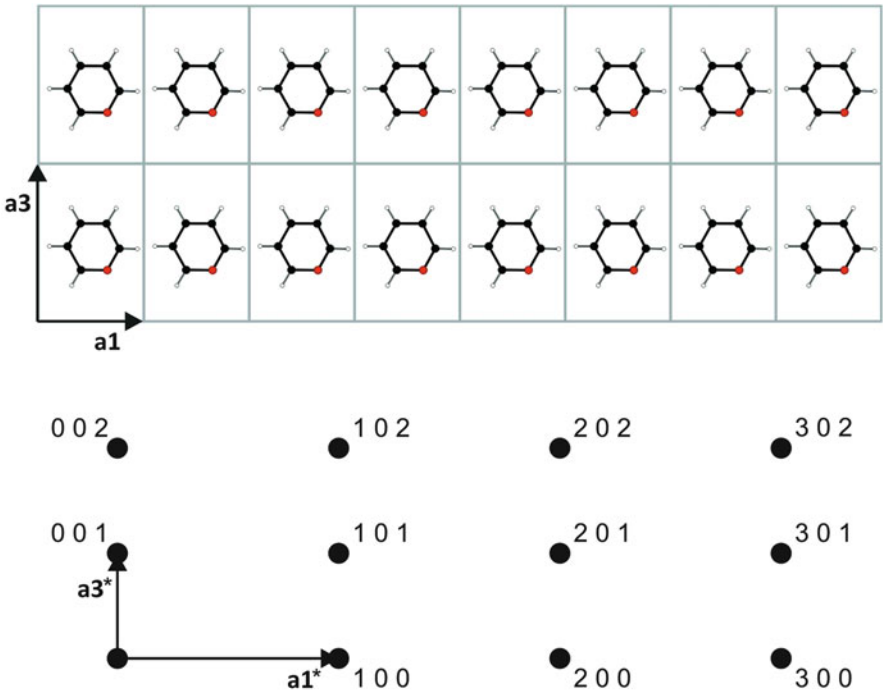

Fig. 2.1 Above: a schematic presentation of an imaginary periodic structure which can be represented as a three-dimensional array of periodically repeated fragments (only a 2D layer is shown for clarity), $\mathbf{a_1}$ and $\mathbf{a_3}$—unit translation vectors defining an elementary cell; Below: simplified periodic diffraction pattern corresponding to the imaginary periodic structure shown above, $\mathbf{a_1}^*$ and $\mathbf{a_3}^*$—unit vectors in the reciprocal space corresponding to the $\mathbf{a_1}$ and $\mathbf{a_3}$ vectors in the direct space. Ratio $\mathbf{a^*_1}$: $\mathbf{a^*_3}$ is inverse to $\mathbf{a^*_1}$: $\mathbf{a^*_3}$. Numbers show the indices of reflections equal to h_1, h_2, h_3 in Eq. (2.1) [2]. Reproduced with permission of the "International Union of Crystallography" from [2]. http://journals.iucr.org/

$$\mathbf{H} = h_1\mathbf{a_1}^* + h_2\mathbf{a_2}^* + h_3\mathbf{a_3}^*, \tag{2.1}$$

where the three vectors $\mathbf{a_i}^*$ in reciprocal space are related to the basic translations $\mathbf{a_i}$ as:

$$\mathbf{a_1}^* = [\mathbf{a_2} \times \mathbf{a_3}]/\mathbf{a_1}[\mathbf{a_2} \times \mathbf{a_3}]; \quad \mathbf{a_2}^* = [\mathbf{a_3} \times \mathbf{a_1}]/\mathbf{a_1}[\mathbf{a_2} \times \mathbf{a_3}];$$
$$\mathbf{a_3}^* = [\mathbf{a_1} \times \mathbf{a_2}]/\mathbf{a_1}[\mathbf{a_2} \times \mathbf{a_3}]. \tag{2.2}$$

There are other structures for which three translation vectors are not sufficient to describe all the diffraction maxima, and additional terms must be added to Eq. (2.1):

$$\mathbf{H} = h_1\mathbf{a_1}^* + h_2\mathbf{a_2}^* + h_3\mathbf{a_3}^* + h_4\mathbf{a_4}^* + \ldots + h_n\mathbf{a_n}^*, \tag{2.3}$$

where $\mathbf{a_i}^*$ and h_i are the reciprocal lattice vectors and integer coefficients, respectively, and the number n is the minimum number for which the positions of the

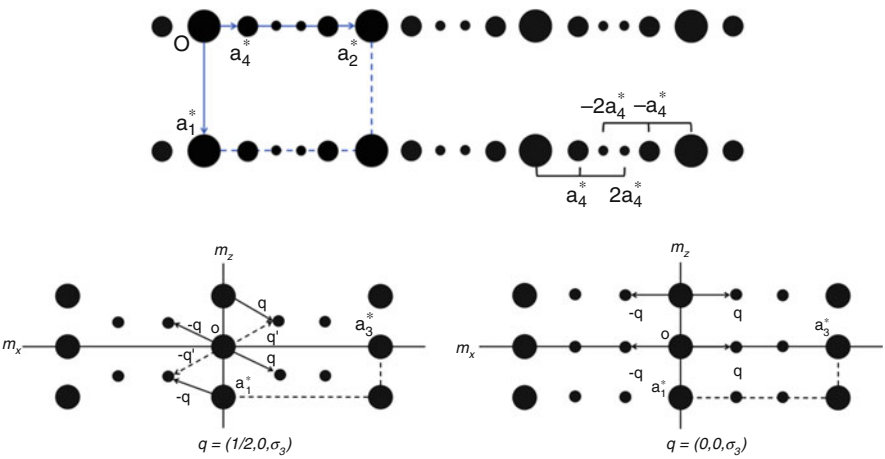

Fig. 2.2 Examples of diffraction patterns of modulated structures: periodic arrays of stronger reflections with weaker satellites [4]

peaks can be described with coefficient h_i. The conventional periodic crystals are a special, though very large, class for which $n = 3$. Crystals for which $n > 3$ are termed aperiodic crystals.

Two fundamentally different types of the aperiodic crystals are known: *incommensurately modulated phases* and *quasicrystals*. The first type relates to periodic crystals: one can find the "main" structural motif, which is periodic, and impose a periodic modulation on this motif, such that the ratio of the two periods is an irrational number. A diffraction pattern in this case will look like a periodic array of stronger reflections with weaker satellites (Fig. 2.2) [4]. The positions of all the reflections can be described as:

$$\mathbf{H} = h_1\mathbf{a_1}^* + h_2\mathbf{a_2}^* + h_3\mathbf{a_3}^* + h_4\mathbf{a_4}^* = h_1\mathbf{a_1}^* + h_2\mathbf{a_2}^* + h_3\mathbf{a_3}^* + m\mathbf{q}, \quad (2.4)$$

where the first three terms correspond to the positions of "main" reflections, and the modulation vector **q** defines the position of the satellites.

$$\mathbf{q} = \mathbf{a_4}^* = \sigma_1\mathbf{a_1}^* + \sigma_2\mathbf{a_2}^* + \sigma_3\mathbf{a_3}^* \quad (2.5)$$

Modulation of the periodicity can be due to a variety of physical phenomena. In some cases modulation arises from variation in the population of positions, conformational and/or orientational variability of molecules as a whole and/or molecular fragments, the rotation of spin, magnetic, or dipole moments, or the incompatibility of the translation periods of different sub-lattices. Incompatibility of sublattices can often arise in the cases where surface layers were grown on a support, or in host-guest compounds, including those where the "host" and "guest" are the same chemical species (Fig. 2.3). There are similarities between modulated structures and structures that contain multiple chemically identical species in the

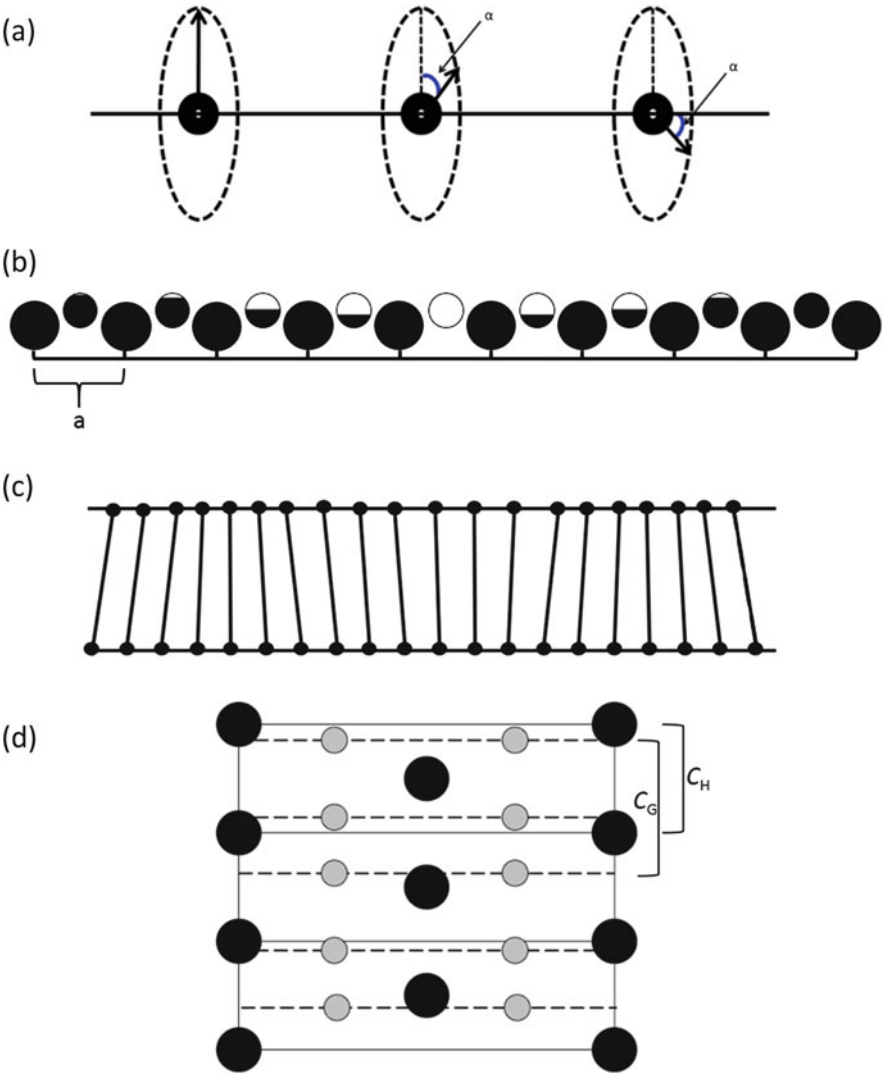

Fig. 2.3 Examples of modulated structures. (**a**) Rotation of fragments, (**b**) modulation of the site occupancies, (**c**) modulation of displacements of species from periodic positions, (**d**) incommensurate translation periods of the sublattices

same unit cell (crystal structures with $z' > 1$) (Fig. 2.4) [2]. Precise diffraction data and skilled data analysis are needed to reliably distinguish between incommensurately modulated structures, structures with disorder, and ordered structures with multiple species in the same unit cell [5].

Aperiodic crystals of this type are fundamentally different from both periodic crystals and from incommensurately modulated phases. Their diffraction patterns

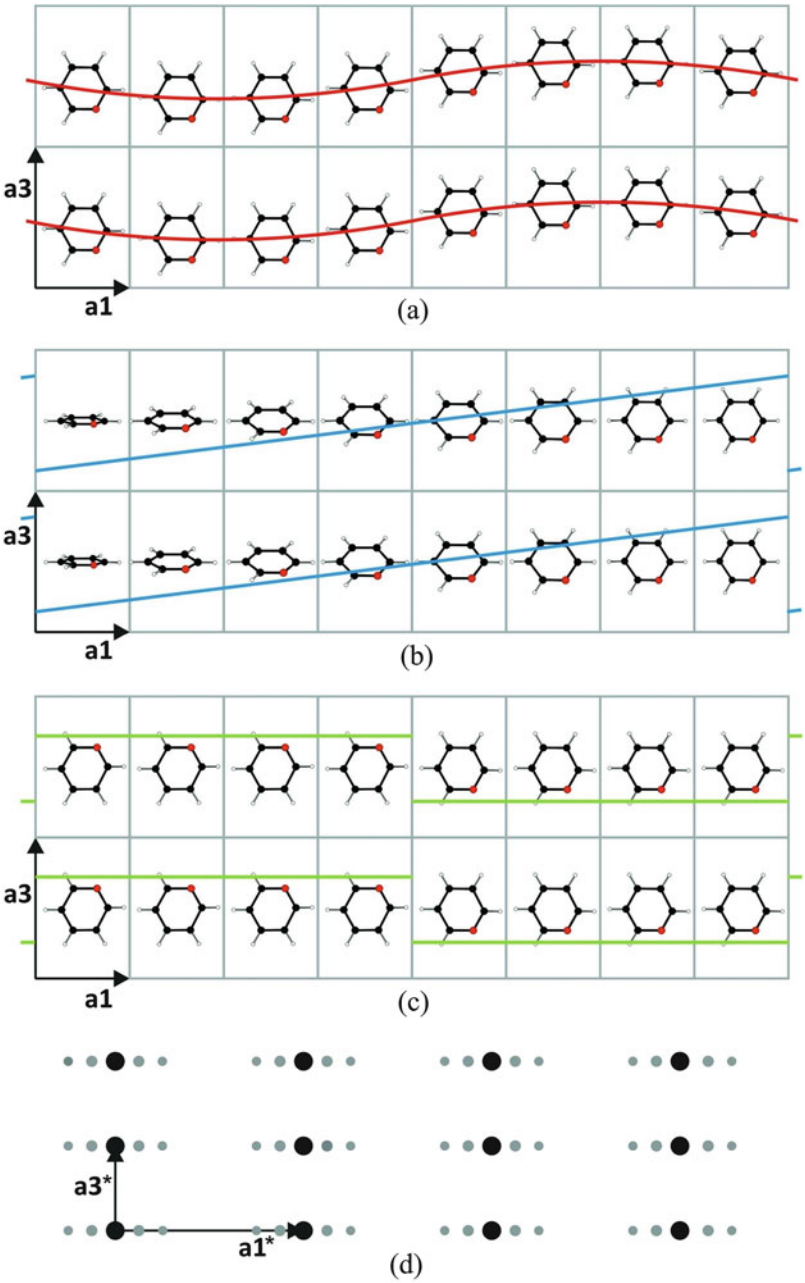

Fig. 2.4 Schematic representation of three variants of a modulated structure with lost translational symmetry along the a_1 axis. All three drawings are derived from the periodic structure shown in the Fig. 2.1 by shifting or rotating the molecules. The atomic modulation functions which can describe the atomic positions are shown as an overlay: (**a**) the molecules are shifted up and down parallel to

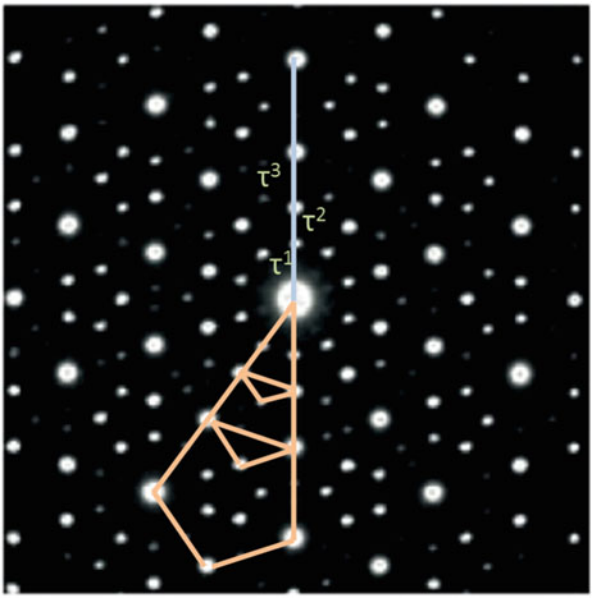

Fig. 2.5 A sample diffraction pattern from a quasicrystal [6, 7]

are characterized by sharp intensity maxima and symmetry that is incompatible with lattice translations (Fig. 2.5) [6]. Such phases were first discovered for some Al-containing intermetallics. Today, examples of the quasicrystalline structures have been reported for various classes of compounds, including organic molecular crystals, polymers and even biomolecules [6–17]. Though very different from periodic crystals, quasicrystals are highly ordered: for any site at some distance from another, the structure is unambiguously defined. Penrose tilings play the same role for describing quasicrystalline structures as Bravais lattices do for describing periodic structures (Fig. 2.6).

Fig. 2.4 (continued) a_2 in a continuous harmonic (sinusoidal) way (**red** curve); (**b**) the molecules are rotated around an axis parallel to a_1, the rotation angle can be described using a sawtooth function (**blue**) with a discontinuity between molecules 8 and 1; (**c**) the molecule adopts two different orientations which can be described by a step-like crenel function (**green**); (**d**) schematic diffraction pattern with satellite reflections (**grey** circles) along a_1*. The modulation proceeds only along a, the c direction is not affected. The number of satellite reflections and their intensity distribution depend on the strength and nature of the modulation. For simplicity, only one diffraction scheme was drawn [2]. Reproduced with permission of the International Union of Crystallography (http://journals.iucr.org/)

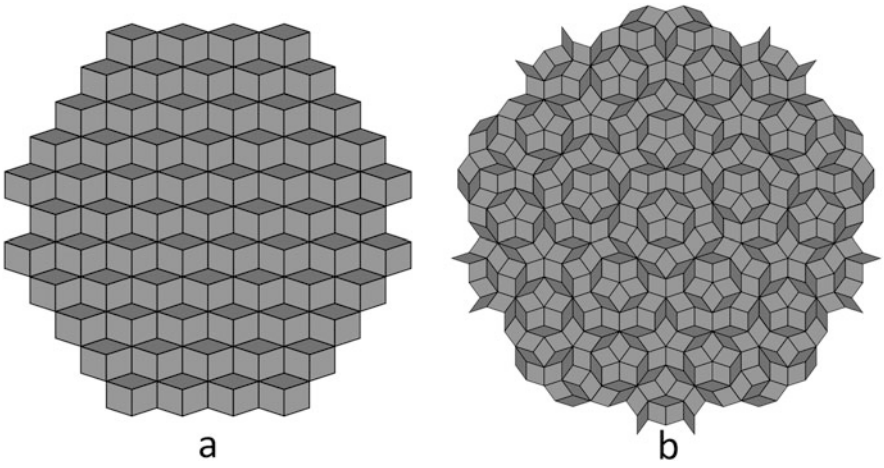

Fig. 2.6 Penrose tilings used to describe periodic (**a**) and aperiodic structures (**b**). In case (**a**) the pattern can be described by a Bravais lattice

2.2 Perfect Disorder (Amorphous Materials)

The structures of both periodic and aperiodic crystals have a common feature: a general law unambiguously defines the structure at any point, i.e. *long-range order* exists. In this respect crystalline structures differ radically from amorphous ones, in which long-range order is absent. This is immediately seen from an X-ray diffraction pattern where no bright diffraction maxima are seen, but instead an "amorphous halo" is present (Fig. 2.7). However, this does not mean that an amorphous structure has no order at all. On the contrary, the structures of amorphous solids are built following certain common, basic principles and can be characterized both qualitatively and quantitatively. In fact, there is often considerable structural order in amorphous solids over length-scales of many Å. The short-range order in amorphous and crystalline solids can be very similar in some cases. This is particularly true in systems such as inorganic oxides [18–21]. However, in other cases, the short-range order differs drastically, e.g. for some organic compounds, where even the molecular structure (conformation) can differ between the crystalline and amorphous phases [22, 23]. The presence of structural disorder in glasses requires statistical structural parameters to provide a spherically averaged description of atomic structure. It is such parameters that are usually measured macroscopically [21].

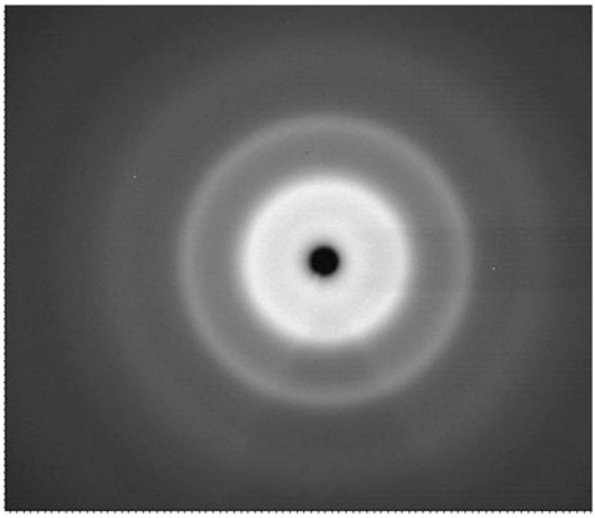

Fig. 2.7 A sample diffraction pattern from an amorphous sample

2.2.1 Radial Distribution Function

The information on local structure, intermediate- and long-range order is contained in the pair distribution function (PDF) g(***r***), also termed pair correlation function (PCF), or radial distribution function (RDF). The RDF in a system of particles (atoms, molecules, colloids, *etc*.) describes the variation in density as a function of distance from a reference particle. In the simplest terms, the RDF is a measure of the probability of finding a particle at distance ***r*** from a given reference particle. The general algorithm involves determining how many particles are within a distance of ***r*** and ***r*** + d***r*** from a particle (Fig. 2.8). The PDF is usually determined by calculating the distance between all particle pairs and binning them into a histogram. The histogram is then normalized with respect to the case where histograms are completely uncorrelated. For three dimensions, this normalization is the number density of the system, multiplied by the volume of the spherical shell. Mathematically, this can be expressed as:

$$g(\boldsymbol{r}) = 4\pi \boldsymbol{r}^2 \rho d\boldsymbol{r}, \tag{2.6}$$

where ρ is the number density. The value of g(***r***) is often plotted as T(***r***) = g(***r***)/*r*, as in Fig. 2.9.

It is clear from a PDF, that an amorphous structure is not "chaotic", but is characterized by short-range order. This order manifests itself in a series of maxima and minima of the PDF at selected distances. In general, the relative intensities and positions of the maxima of a PDF are characteristic for an amorphous structure. It contains considerable detail about the structural order surrounding each type of atom: positions of peaks give the radii of successive shells of atoms surrounding the average atom and the areas of the Gaussian peaks yield the number of atoms in each

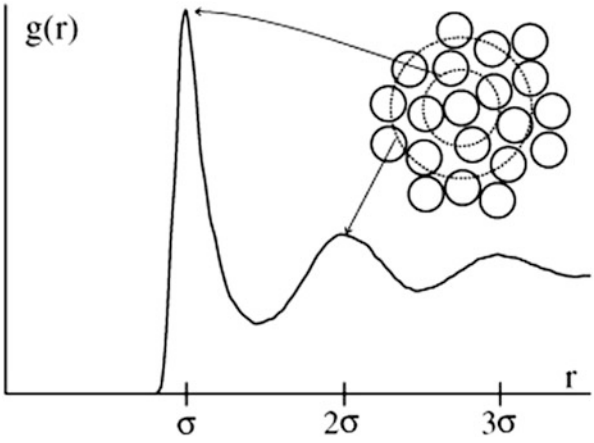

Fig. 2.8 A schematic illustration of the general algorithm of calculating a RDF (the number of particles within a distance of r away from a selected particle) [24]

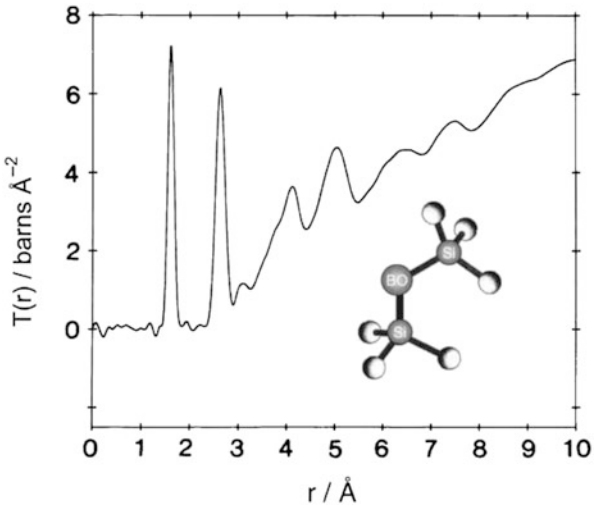

Fig. 2.9 An example of the radial distribution function: the normalized correlation function T(r) = g(r)/r characterizing a silica glass (obtained by neutron scattering). The first three peaks correspond to Si–O, O–O and Si–Si correlations, respectively [20]

of these shells [21]. For example, the first three peaks of the PDF for silica glass (Fig. 2.9) correspond to Si–O, O–O and Si–Si correlations.

One can determine g(***r***) indirectly using neutron scattering or X-ray scattering data [21–23, 25–43]. It is derived from the measured scattered intensity, I(Q), by Fourier transforming the normalised X-ray or neutron structure factor S(Q). Here, Q is the scattering vector $4\pi\sin\Theta/\lambda$, 2Θ is the scattering angle and λ is the X-ray or neutron wavelength. The technique can be used to probe structure at very short length scales (down to the atomic level), but involves significant space and time averaging (over the sample size and the acquisition time, respectively). In this way, the radial distribution function has been determined for a wide variety of systems, ranging from liquid metals to charged colloids [44–49]. It should be noted that