Solid forms of pharmaceutical molecules

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1. Introduction

A drug discovery is characterized by two stages. The first in terms of time is called „lead structure“, followed by a so called „drug candidate“ stage. The lead structure stage involves selecting the optimum molecule of the pharmaceutical, while drug candidate stage means selecting the optimum solid form. Usually, 5 – 10 candidates pass to the drug candidate stage and the result is the selection of the final solid API (Active Pharmaceutical Ingredience) for the ensuing formulation of the solid dosage form. The lead structure stage concerns only the discovery of the original drug, the drug candidate stage may concern also generics (a drug which is bioequivalent with original and is produced and distributed after the patent protection of the original).
The choice of the optimal API for a specific solid drug formulation means the optimization of its properties. The most important properties of API include its solubility, dissolution rate and permeability, which are closely related to the oral bioavailability of the drug. Apart from these, there are other properties influencing functional and technological parameters of the API and its patent non-collision status (Table I).
For the selection of the optimal API, several dozens of solid forms may be available from one molecule. An example is atorvastatin calcium, a drug used for the treatment of high cholesterol, for which more than 60 solid forms are patented [1]. Piroxicam, a non-steroidal anti-inflammatory drug, was synthesized in more than 50 forms [2] and more than 100 forms are described for sulphathiazol [3], a local antimicrobial agent. A review of possible chemical and physical types of pharmaceutical solid forms is given in Table II. In the case of multi-component compounds the reduction in number of solid forms is given by the condition of pharmaceutical acceptability of the fellow component (e.g. counterion in the case of salts), see GRAS (Generally Recognized as Safe [4]).

2. Polymorphs

Most pharmaceutical molecules are polymorphic. Polymorphism (from Greek: *polys - multiple, morfé - shape*) is an ability of a chemical compound to crystallize – depending on crystallization conditions – in different crystal structures alias polymorphs. Molecules in the crystal structure of a polymorph are bonded by weak interactions (H-bridges, Van der Waals forces, π-π interactions). Two general categories of polymorphism are distinguished: packing polymorphism and conformational polymorphism. Packing polymorphs which differ by molecules packing in the crystal structure, are formed by a rigid molecule (e.g.. sulphapyridine) while a flexible molecule existing in various conformers forms conformational polymorphs (e.g. L-glutamic acid).
In practice mixed types of polymorphism are often encountered. Labelling of polymorphs is not unified (e.g. I, II, III …; A, B, C…; α,β, γ) and it occasionally happens that identical polymorphs are named differently by different discoverers. The polymorphism of anhydrates (ansolvates) means that water molecule is not involved in the crystal structure of the polymorph. The polymorphism of hydrates (solvates) is called pseudopolymorphism or

solvatomorphism.. Polymorphs may or may not differ by their crystal shape (habitus). An ability of a compound to form different crystal shapes, while its crystal structure remains the same, is not polymorphism, but crystal morphology (crystal design). Fundamental causes of polymorphism are not known. But a statement by W. McCrone from 1963 is ever confirmed that if a molecule becomes a focus of attention, further polymorphs are discovered. An example can be olanzapine intermediate, the so-called ROY (red-orange-yellow), Fig. 1, which is already described in 10 polymorphs [5]. On the other hand a very well-known and many times crystallized molecule of sucrose is monomorphous.

Among pharmaceutical molecules, the most frequent case is dimorphism. A well-known example is the patent litigation between pharmaceutical companies Glaxo and Novopharm over two polymorphs of ranitidine hydrochloride [6], which decreases the production of stomach acid, or the problems of the company Abbot Laboratories concerning two polymorphs of ritonavir [7] – an inhibitor of HIV-protease. Since polymorphs differ by their crystal structures, they differ by their properties, of which solubility and dissolution rate are the most important. A typical ratio of solubility (beware various definitions of solubility) of two polymorphs is less than two, but there are exceptions, e.g. polymorphs of premafloxacin I/III or polymorphs of chloramphenicol A/B have this ratio larger than 10 [8]. Thus it can happen that a less soluble polymorph does not even reach the minimum medicinal concentration in blood.

An unwanted polymorph in the mixture is called a polymorph impurity. In a polymorph system only one polymorph is thermodynamically stable, the other are unstable. The stable polymorph is characterized by the lowest Gibbs energy, the lowest solubility in any solvent, the lowest dissolution rate and the lowest reactivity. For a drug formulation the original companies usually choose a stable polymorph, the generic companies then have to use even an unstable and less-lasting polymorph.

Uncontrolled phase transitions of unstable polymorphs into more stable ones are a big problem of pharmaceutical industry. Two types of polymorphous transitions are distinguished, the enantiotropic and the monotropic (Fig. 2). The enantiotropic transition is characterized by the transformation temperature $T_{A\rightarrow B}$ at which an originally more stable polymorph A transforms into a finally stable polymorph B. The enantiotropic transition is often reversible and well-defined. The monotropic transition in solid state has no transformation temperature, so that the polymorph transition pass over the liquid phase. In practice this means the crystallization from a different solvent. Unfortunately, the polymorphous transitions of pharmaceutical substances are more often monotropic than enantiotropic and moreover hysteretic.

Uncontrolled polymorph transitions in pharmaceutical manufacture may happen during the final crystallization of API, during long-lasting standing of the product in the parent solution, during drying, micronization, tablet pressing, during wet granulation, or even in the tablet during storing. The most important for the production of the wanted polymorph is the final crystallization and the monitoring of all its parameters (Table III) to prevent a potential creation of an unwanted polymorph. Since there are many variable parameters and it is difficult to monitor them all in cases of sensitive polymorph systems, a method of seeded crystallization is often used. In this case seeds of requested product which act as nuclei are added to the oversaturated solution. On them then the product grows.

For pharmaceutical companies, the problem of polymorphism is rather a blocking than a creative element. Sometimes the differences between two polymorphs are tiny and tiny are the differences in properties (e.g. polymorphs of aspirin - acetylsalycilic acid [9]). Nevertheless,

polymorphism is closely watched by regulatory authorities and no pharmaceutical manufacturer can afford to ignore it.

3. Anhydrates and hydrates

The first choice of API for a solid drug formulation is the anhydrate of active substance (free acid, free base or neutral compound). Anhydrates together with salts form the majority of all drug formulations. If the anhydrate for some reason is not suitable (e.g. it is little soluble, unstable, has complicated polymorphism etc.), then possible hydrates are monitored. The hydrate is most frequent a solvate containing water molecules in its crystal structure. Water molecules can be incorporated in the structure in a stoichiometric manner (stoichiometric hydrates) or non-stoichiometrically (non-stoichiometric hydrates), Fig. 3. For the formulation stable stoichiometric hydrates in a lower stage of hydration are chosen in which water molecules are bound to molecules of the active substance by H-bonds. The dehydration of a stoichiometric hydrate often results in the collapse of the crystal structure and the origin of an amorphous phase. Non-stoichiometric hydrates are not suitable for the formulation because the water content in them changes with the partial pressure of water vapour in the ambience and with temperature a thus they difficult to define. In non-stoichiometric hydrates, water is not bound very firmly, it rather fills present cavities in the structure without forming H-bridges. The dehydration of non-stoichiometric hydrates does not result in the origin of an amorphous phase but a crystalline anhydrate originates. An example of a non-stoichiometric hydrate are the interstitial water molecules in the cavity of β-cyklodextrin [10].
Other solvates (with the exception of ethanol solvates) are not used for the formulation but can be used as important precursors. For instance polymorhs which are otherwise difficult to attain can be obtained by their desolvation.
The stability of the system anhydrate/hydrate depends on the ambient relative humidity. Many active substances form hydrates, often in a various degree of hydration and stability. If the hydrate is the more stable in the system anhydrate/hydrate then the hydrate has all available reliable proton donors and acceptors better satiated compared to anhydrate (Etter′s rule [11]). For instance ergot alkaloid tergurid exists as an anhydrate, a twothird hydrate and a monohydrate, and the stable phase is the monohydrate [12], Fig. 4. Tergurid tends to form hydrates eagerly which results in taking up residual water molecules from acetone during crystallization. Formulations from hydrates are not very frequent and represent only several per cent of the total number of APIs (e.g. chloral hydrate, levofloxacin hemihydrate, terpin hydrate and others). The reason is their thermal instability and possibility of the potential dehydration during drying. Of excipients, much used is the lactose monohydrate.

4. Salts

About a half of all APIs used today are salts. Salts represent a considerable enlargement of the portfolio of solid forms of pharmaceutical molecules. Salts are stable and well soluble in polar solvents (first of all in water), because they contain ionic bond. A necessary prerequisite for the formation of salts is the presence ionizable groups in the molecule (Fig.5). A pharmaceutical substance then can be in the API either in the form of cation (about 75% of pharmaceutical salts) or in the form of anion (about 25% of pharmaceutical salts). The

counterpartners must comply with the pharmaceutical acceptability (see GRAS). At present 69 cations and 21 anions comply [13].
The most frequent counteranion is hydrochloride, followed by sulphate and hydrobromide. Only then occur organic anions, most often tartrate, mesylate (methansulfonate), maleate and citrate. The most frequent countercation is sodium ion, followed by Ca^{2+}, K^{+} and Mg^{2+} ions, and only then comes the first organic ion, meglumine (N-methyl-D-glucamine). Na-salts are mostly so well soluble that they are used also in injection applications. There is one more essential advantage of salts – their solubility is a function of pH. Since pH in the gastrointestinal tract (GIT) vary between 1-7,5 (e.g. in stomach pH is 1-3, in small intestine it is 5-7), it is possible to optimize in GIT the location with the highest solubility by selection of suitable salt. Each salt has a pH_{max} value with the maximum solubility.
The choice of an optimum salt for the solid drug formulation does not mean only finding a substance with the maximum solubility, but also with maximum stability. With growing solubility, diffusibility rises and stability decreases. The substance is easily diffusely dispersed in the organism and penetrates biological membranes. As a result it is less specific as to the site of action and eliminates more readily.
Salts show polymorphism as well but not so effuse as in the case of free acid, free base or neutral compound. The problem of polymorphism can be circumvented by choosing a suitable salt. For instance the ergot alkaloid terguride crystallizes in 7 forms as a base, while converted to salt we obtain only one monomorphous tergurid hydrogenmaleate monohydrate. The crystallization of API in the form of a salt can be used for the separation of the active substance from the mixture or for its purification. For instance a liquid valproic acid forms solid Na- and Mg-salts.
In a mixture of two or more API it is necessary to consider their mutual interaction. For instance the analgetic proxyfen was originally formulated as a hydrochloride and used together with aspirin in one formulation. But aspirin decomposed easily in the presence of propoxyfen hydrochloride, it was unstable. Only after re-formulation of propoxyfen into napsylate aspirin stabilized (brand name Darvocet, marketed by Elli Lilly) [14]. Moreover, propoxyfen napsylate is more stable and less toxic compared to hydrochloride. Salts may also form hydrates which can be also used for the formulation. The best known example is atorvastatin calcium trihydrate (Sortis, Pfizer).

5. Cocrystals

Cocrystals are at present the most dynamically developing group of solid pharmaceutical substances. The definition of the term “pharmaceutical cocrystal” is still under discussion, but essentially it is a multi-component compound that is formed between a molecular or ionic API and a cocrystal former that is a solid under ambient conditions [15], Fig. 6. Pharmacodynamically, cocrystal former is a ballast molecule (the same applies to salts), and the GRAS rules apply. Nevertheless even a cocrystal former can be an active molecule.
The stoichiometric ratio of API and cocrystal former in a pharmaceutical cocrystal is mostly simple (1:1, 1:2, 1:3 or vice versa). Cocrystals are not necessarily binary compounds, ternary and quarternary cocrystals are known. Cocrystals can be divided into: cocrystal anhydrates, cocrystal hydrates (solvates), anhydrates of cocrystals of salts and hydrates (solvates) of cocrystals of salts. The borderline between salts and cocrystals is blurred and can be distinguished by the location of the proton between an acid and a base. In salts, carboxyl proton is moved to the hydrogen of the base while in cocrystals the proton remains on the

carboxyl of the acid. In cases when ΔpKa = pKa(base) - pKa(acid) = 0 – 3 , the transfer of proton is ambiguous and we talk about the salt-cocrystal continuum [16].
The cocrystallization potential of some active molecules is studied in detail, e.g. carbamazepine, itraconazole, piroxicam, norfloxacin, fluoxetin, caffein and others. [17]. The reason is to achieve a wide variation in solid-state properties of APIs. These efforts stem from principles of supramolecular chemistry and crystal engineering to affect the properties of API through the „bottom up“ approach. This is illustrated in the following examples. By the cocrystallization of antifungal drug itraconazole with 1,4-dicarboxylic acids (succinic acid, L-tartaric acid or L-malic acid) a modification of the dissolution profile is achieved compared to the amorphous form of itraconazole (Sporanox, Janssen-Cilag) [18]. A 1:1 carbamazepine/saccharin cocrystal compared to polymorph III of carbamazepine (anticonvulsant Tegretol, Novartis) shows no polymorphous behaviour and is not prone to hydration [19]. The cocrystallization of pregabalin with S- mandelic acid separates from the mixture of R and S isomers only the (1:1) cocrystal (S)-pregabalin/(S)-mandelic acid. This technology is used by Pfizer in manufacturing dosage form Lyrica [20]. The cocrystals of paracetamol show an improved tablet formation ability than free paracetamol, polymorf I (Panadol, GlaxoSmithKline) [21]. Caffein tends to form hydrates at high RH (relative humidity) while its cocrystals with oxalic acid or malonic acid do not have this unwanted property (never form hydrates) [21]. However, general trends of variation of properties during the transition from APIs to their cocrystals are not so far evident because fundamental causes of cocrystallization are not known so far.
The preparation of cocrystals involves a number of techniques, in gas, liquid or solid phase. The most important is the joint cocrystal growth from solution or joint solidstate grinding, often with the addition of a small amount of a „molecular lubricant“ (methanol, cyclohexan, chlorophorm etc.). Furthermore, co-crystals can be synthesized by evaporation, sublimation, melting, sonication etc. It often holds that identical starting components may not yield the same product under different cocrystallization techniques.
Although cocrystals are intensively studied and patented by both academic institutions and R&D departments of pharmaceutical companies, there is no medicament on the market formulated from a cocrystal. Nevertheless it turns out that some pharmaceutical salts should be re-classified as cocrystals. This is also important for patent litigation.

6. Glycosylated derivatives

Glykosylated derivatives (acetals of saccharides) are not usually ranked among solid forms of pharmaceutical molecules in literature [22]. Certainly unjustly because in natural materials the molecules of active substances are often bonded to saccharides, e.g. digitoxin in the plant *Digitalis lanata*.
Glykosylated derivative can be obtained by adding saccharide (sugar) component to the molecules of active substances through a glycosidic bond , Fig. 7. This bond can be formed if a hydroxyl group is present in the molecule of the active substance which is bonded to the hemiacetal group of a saccharide. The presence of a saccharide component containing several OH-groups often increases solubility of API in polar solvents.
Moreover, the glycosylation often improves also pharmaco-dynamic properties of the active substance. A well-known example is the antibiotics vankomycin some of whose glykosylated derivatives are 500 times more efficient compared to vankomycin itself [24]. Apart from saccharides, it is possible to bond for instance peptide, or protein to the molecule of active

substance and thus to change dissolution profiles and pharmaco-dynamics of these derivatives.

7. Amorphates

Amorphous forms are thermodynamically metastable which results from the disordering of their inner structure on molecular level. Compared to ordered crystalline phases, amorphates have better molecular mobility which results in a better dissolution profile and thus a better oral bioavailability. On the other hand this is compensated by lower chemical and physical stability (shorter expiration) and by greater demands on production and storing (e.g. protecting atmosphere).

An empirical rule applies to amorphates: the temperature of storing must be 50^{o} C below the temperature of their glass transition T_g [25]. The amorphous state has a higher energy than the crystalline state and therefore amorphous phases tend to turn into crystalline ones. The crystallization of amorphates is facilitated by their high hygroscopicity and absorbed water acts as a plasticizer increasing molecular mobility. The transition between amorphous and crystalline phases is not sharp and so called semicrystalline phases appear, e.g. atorvastatin calcium, V (Teva). [26].

Tiny differences between amorphous phases of one API (e.g. different methods of synthesis) initiate discussion about polyamophism (the ability of a substance to exist in several different amorphous forms). Polyamorphism is well defined in inorganic phases (e.g. six- and four-coordinated amorphous silicon) but no polyamorphates have been so far proved in pharmaceutical substances. Current formulations from amorphous phases include asthma medicine, e.g. zafirlukast (Accolate, Astra-Zeneca [27]), quinapril hydrochloride (Accupro, Accupril, Pfizer [28]), anti-fungal drug itraconazole (Sporanox, Janssen-Cilag [29]) or non-steroidal anti-inflammatory drug indomethacin.(Indocin, Merck [30]. In solid drug formulations, amorphates are stabilized by suitable excipients (e.g. PVP, trehalose, sorbitol, etc.).

Depending on temperature and ambient relative humidity the water content in amorphous phases varies. However, pharmaceutical phases denoted as amorphous hydrates have been patented lately, e.g. amorphous esomeprazole hydrate [31], amorphous cephalosporine hydrate [32] or amorphous imatinibe mesylate hydrate [33]. Although a physical and chemical substance of the term amorphous hydrate is debatable, we can admit that in certain cases a relatively stable amorphous phase containing a defined amount of water may exist.

8. Conclusion

The portfolio of solid forms of pharmaceutical molecules is nowadays very wide and somehow difficult to overlook. A further increase in number of new co-crystals, or multi-component compounds generally, and their application in solid drug formulations are expected in future. Progress in the theory of chemical bond, prediction of crystal structures and the development of supramolecular chemistry enable better understanding of the fundamentals of polymorphism and control of crystallization processes. This will lead to a better orientation and targeted selection of the optimum solid form of a certain pharmaceutical molecule with requested technological and functional properties.

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