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Design of Pharmaceutical Cocrystals for Drug Solubility Improvement

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Abstract—The new technology of enhancement of the solubility of poorly soluble drug substances is based on the synthesis and application of cocrystal pharmaceutical systems. The solubility and bioavailability of such systems are several orders of magnitude higher than those for the individual compounds and much higher than the respective parameters attainable by other technologies.

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INTRODUCTION

The highly biologically active drug substances developed over the past few decades are almost insoluble in aqueous media. About 30% of drugs that have successfully gone through preliminary biological tests, fail to pass clinical trials because of unfavorable characteristics (adsorption, distribution, metabolism, excretion). This procedure of drug development is quite time-consuming and adds much to the cost of the final product. In this connection a necessity arises to develop scientific foundations for the creation of soluble forms of drugs. This problem can be solved by searching for regularities in the change in the physicochemical properties of compounds that exist as crystals and pass into solution. The available theoretical and experimental evidence on correlation between the crystal structure, physicochemical properties, and pharmacological activity of compounds opens up the possibility not only for targeted structural modification of known drug, aimed at improving their properties, specifically solubility, but also aids in the search for principally new biologically active compounds.

There are various methods to enhance drug solubility. Of them we would like to mention structural modification of the molecules (to decrease the energy of crystal lattice) and preparation of pharmaceutical cocrystals.

Biopharmaceutical Drug Classification System

The bioavailability of drug is characterized by two key parameters: solubility and membrane permeability. Based on these two parameters, Amidon et al. [1] proposed the so-called biopharmaceutical drug classification system (Fig. 1). According to this system, all drugs can be arbitrarily divided into four classes in terms of their potential applicability. Class I drugs exhibit high solubility and permeability, they hold a great promise for application. Class II drugs, too, have certain perspectives, provided their solubility parameters are corrected. The following approaches to solubility correction have been reported: preparation of salts [2], reduction of particle size [3], introduction of nucleation inhibitors [4], design of metastable polymorphous modifications [5, 6], synthesis of solid dispersions [7], complex formation [8], and cocrystal [9, 10] and lipid technologies [11]. Class III drugs require correction of membrane permeability (synthetic stage of structural correction). This problem is usually solved by using prodrugs [12], locomotive molecules which ensure drug permeation through membrane [13], etc. Finally, Class IV drugs cannot be applied without special delivery systems. As a rule, their oral formulations are completely inefficient, and, therefore, alternative administration routes, for example, intravenous, should be used.

About 40% of drugs marketed in European countries, USA, and Japan are almost insoluble in aqueous media [14]. Table 1 shows the shares of marketed drugs and drugs that are under trials/development in pharmaceutical companies [15]. Class II is the most abundant (30% marketed drugs and 60–70% drugs under development). Just this class attracts the greatest

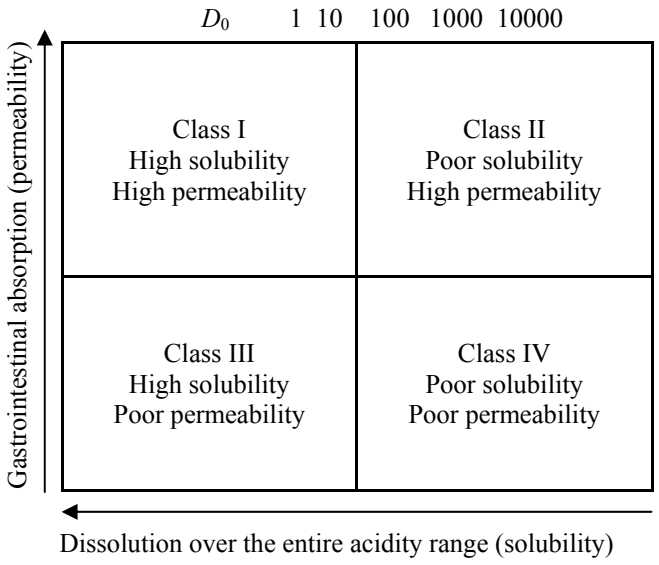

Fig. 1. Biopharmaceutical classification system of compounds [1]. $D_0 < 1$ relates to highly soluble compounds, $D_0 > 1$ relates to poorly soluble compounds; $D_0 = 1000$ shows how many times the volume of a pharmaceutically significant solvent should be increased to dissolve one dose of a drug compared to the drug with $D_0 = 1$.

attention of many pharmaceutical companies, since the solubility correction of drugs that have passed pre- and clinical trial cycles does not require essential financial investments and time consumption for the product to be launched on market.

Design of Molecular Corystals for Solubility Enhancement

The design of molecular crystals that can be used as crystalline pharmaceutical materials is not infrequently aimed at enhancing the solubility and solution rate of drugs. To this end, a necessity arises to modify the surface and molecular packing of crystals contacting the medium.

Table 1. Distribution of drug classes on the market and under development

Drug class[a]	Solubility	Permeability	Shares of drugs, %	
			on the market	under development
I	High	High	35	5–10
II	Low	High	30	60–70
III	High	Low	25	5–10
IV	Low	Low	10	10–20

[a] According to the biopharmaceutical drug classification system [1, 15].

Polymorphous Forms

Enhanced solubility is characteristic of unstable/metastable polymorphous forms with retained molecular structure [16, 17]. Such polymorhs have a lower energy of crystal lattice, due to which they have a higher thermodynamic solubility.

A great number of studies have been published to show that polymorphous modification affects the solution rate and/or bioavailability of drug substances. Among such publications we can mention those focused on the crystal forms of phenobarbital [18], spironolactone [19], and carbamazepine [20], whose metastable crystal forms display enhanced solubility. It was found that two different polymorphs of phenylbutazone dissolve at different rates [21]. Singhal and Curatolo [22] gave examples illustrating the difference in the pharmacokinetic profiles of different polymerphous forms of carbamazepine and oxytetracycline.

In whole, according to published data, unstable polymorphous forms are no more than two times more soluble than stable forms [22].

Cocrystals

An alternative approach to increasing the solubility, solution rate, and bioavailability of compounds is cocrystallization, a method which is historically classed with formation of molecular complexes. Over the past years there has been active work on the theory of the development of pharmaceutical cocrystals and crystal solvates.

Cocrystals represent supramolecular systems (Fig. 2) in which one component is a poorly soluble active pharmaceutical ingredient (API) as one component and the second component is a readily soluble compound fully digested in the body and involved in enzymatic reactions. Such readily soluble substances (coformers) are recommended for use in the food and pharmaceutical industries.

The crystal forms of APIs traditionally restricted to salts, polymorphs, and solvates (including hydrates). Cocrystals form an abundant class of crystal structures. Their prototype is quinhydrone described as early as in the middle of XIX century [23]. It should be noted that the term “cocrystal” is heavily debated in the literature [24]. For example, according to the general definition, a cocrystal is a combined crystal or a crystal comprising two different molecules [25]. Aakeröy and Salmon [26] gave the following clarification: a

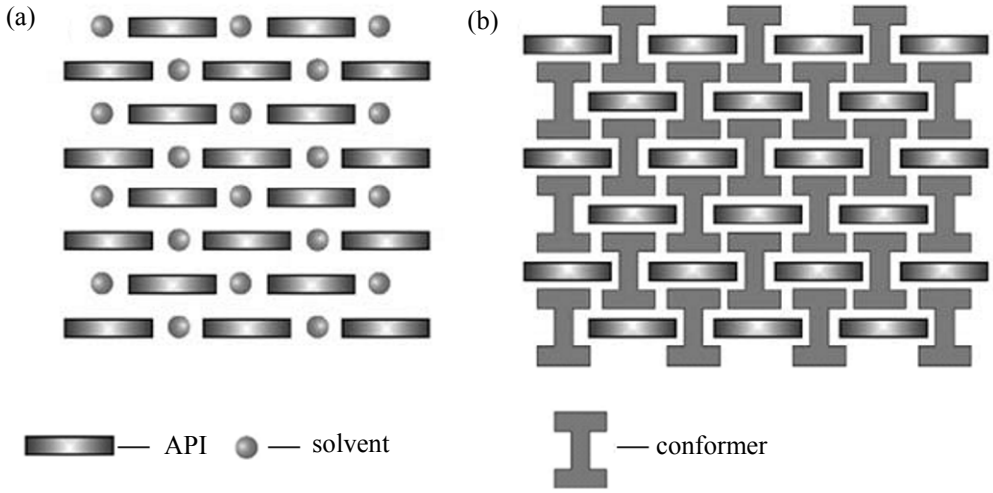

Fig. 2. Schematic representation of pharmaceutically significant binary crystal systems: (a) crystal solvate; (b) cocrystal (the figure has been borrow from [52]).

cocrystal is formed by reagents which are crystals at standard conditions. As a result of numerous discussions, a pharmaceutical cocrystal was defined as a cocrystal formed by a molecular or an ionic API and a conformer which is solid under standard conditions. Systems comprising two components that are both crystals under normal conditions are known for a fairly long time but under different names, such as addition compounds [27], organic molecular compounds [28], molecular complexes [29], solid complexes [30], mixed binary molecular crystals [31], or heteromolecular crystals [32].

Even though cocrystals have first been mentioned long ago, they are still scarcely studied. For comparison, the Cambridge Structural Database (CSD) by August 2005 contained as little as 1487 cocrystals against 35882 hydrates. However, the interest in cocrystals is constantly growing. Thus, in 1990 about 20 cocrystals were described, whereas in 2003 they already amounted more than 150 [33]. The number of cocrystals included in the CSD in 2007 was more than 250 [34].

Thus, drug and prodrug cocrystals represent a new type of materials attractive for research and application in pharmaceutics. Cocrystals are only a part of a broader family–multicomponent complexes–including also salts, solvates, cluthrates, inclusion compounds, and hydrates (Fig. 3).

The principal difference between crystal solvates and cocrystals consists in the physical state of their isolated, free components. If one of the components is a liquid under normal conditions, thy crystal is defined as crystal solvate. If both components are solids at room temperature, this system is defined as cocrystal. Even though, at first glance, this difference might seem of little consequence, it nevertheless affects the preparation and stability of such systems. As a rule, crystal solvates are easier to prepare than cocrystals [35].

Cocrystals are attractive in that they make it possible to prepare new crystalline API forms with desired properties (for example, enhanced solubility, thermodynamic stability, improved mechanical properties, etc.). The possibility to choose components for a cocrystal much facilitates the “fine tuning” of its physicochemical properties [36]. It may be no accident that Trask [37] stressed that cocrystallization is a fruitful field of materials research with a direct output of the results to the pharmaceutical industry.

The questions concerning cocrystal formation are considered at early stage of their research. How does a cocrystal form? What additional hydrogen bonds form and break during formation of a new compound? To answer such question, numerous works have been undertaken [38–41], in which the authors analyzed intramolecular bonds between cocrystal components.

The physicochemical theory underlying the design of cocrystals is based on the supramolecular synthon paradigm. The probability of cocrystal formation essentially increases if the process involves generation of heterosynthons to replace the homosynthons present in the crystal structure of the individual components (heterosynthons are suggested to be preferred by energy). In

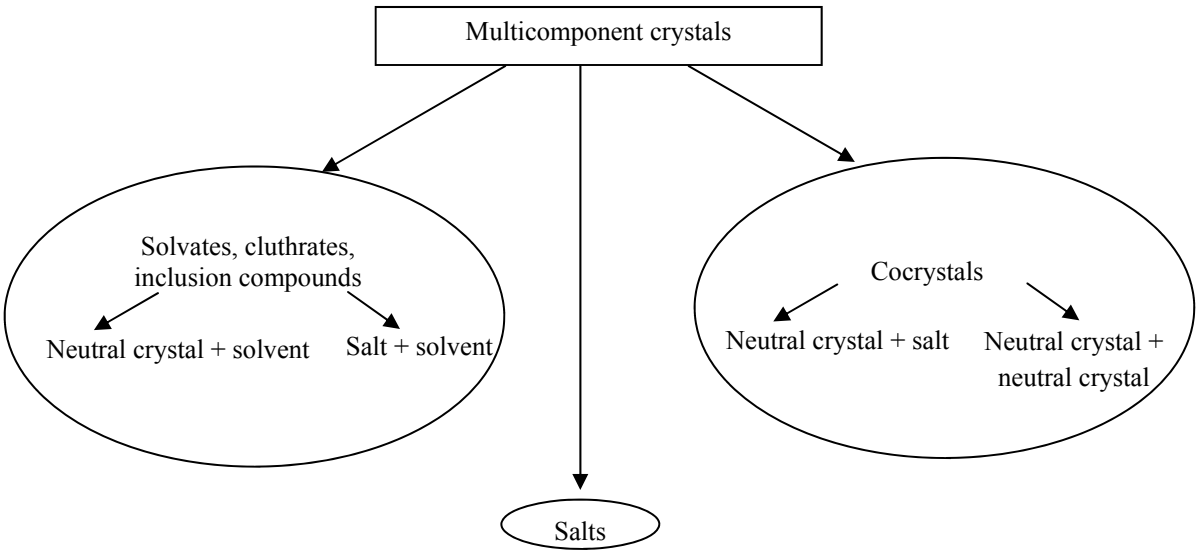

Fig. 3. Types of multicomponent crystals [35].

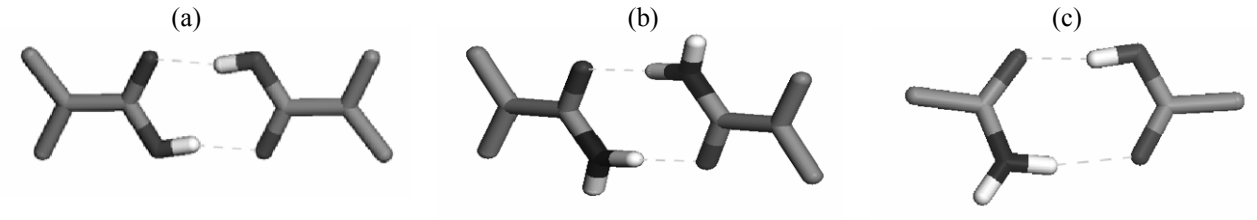

Fig. 4. Supramolecular acid–amide synthons: (a, b) supramolecular homosynthons on an example of (a) acid and (b) amide dimers; (c) supramolecular heterosynthon on an example of an acid–amide dimer [41].

view of the fact that amides and acids are widely represented in the CSD, just these compounds have come under the scrutiny of researchers dealing with cocrystal design and synthesis. Actually, a lot of compounds capable of forming cocrystals have an acid–amide supramolecular heterosynthon in their structures (Fig. 4). For example, the CSD in 2004 contained 118 of such crystal structures having both amide and acid groups.

The acid–amide synthon is not the only example of a strong supramolecular heterosynthon, which is more preferable than the parent homosynthons. Fleischman and co-workers [42, 43] underlined how important is to realize the role of supramolecular synthons on cocrystal formation.

Cocrystal Screening Algorithms

Synthesis of pharmaceutical cocrystals with preset properties is a probabilistic process. To control this process, one needs clear criteria and methods for prompt and efficient detection of cocrystal formation and measurement of the physicochemical characteristics of the product. Moreover, according to the key conceptual principles of the green technology, the highest possible levels of the cost effectiveness and environmental friendliness of the process should be provided [44]. In other words, the basic requirements to a technology for cocrystal production include low consumption of power and materials; minimum solid/liquid wastes; no organic liquids as solvents and carriers; no hazardous reagents and materials; no gas-phase processes; low production scale; and high selectivity.

Cocrystals are synthesized by a wide variety of methods. Figure 5 shows the shares of different methods of cocrystal synthesis among those reported in the literature.

As seen from Fig. 5, cocrystals are most commonly synthesized by slow evaporation from solution. However, this method does not meet the green-technology criterion because of the high solvent consumption. Traditional methods of synthesis of cocrystals from solution are fairly time- and labor-

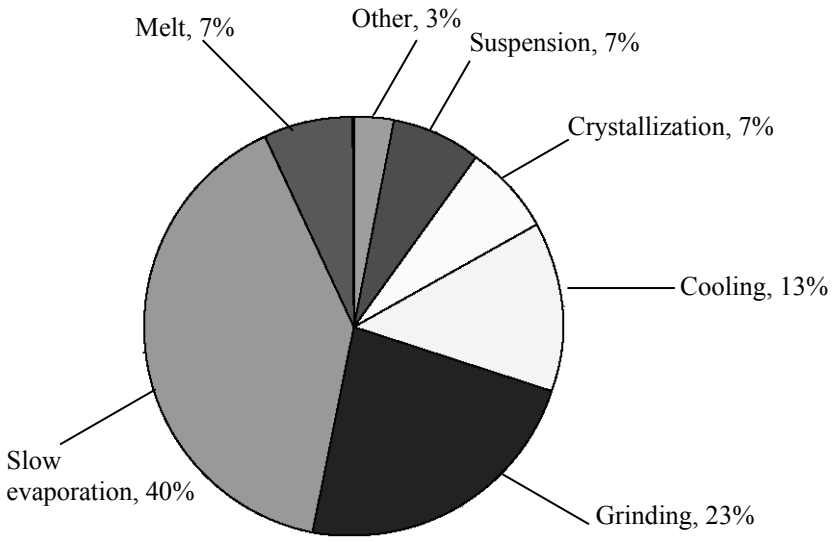

Fig. 5. Breakdown of techniques used for cocrystallization [45, 49].

consuming and scarcely suitable for screening, as screening approaches envision rapid synthesis and analysis of series of samples. This requirement is best met by dry grinding, grinding in the presence of liquids, and crystallization from melts [44, 46, 47]. The main advantage of these methods is an almost complete absence of solvents from the technological process, which reduces reagent costs and shortens the time of cocrystal formation.

Differential scanning calorimetry (DSC) with monitoring heat effects associated with phase transitions, too, is used for cocrystal screening. Many organic binary systems feature melting of eutectic mixtures on heating, and this suggests the possibility of cocrystal formation in the eutectic point. The observation in the DSC curves of invariant endotherms (assignable to eutectic and cocrystal) independent of the composition implies cocrystal formation (Fig. 6). The principal limitation of the DSC screening is that its results are impossible to interpret unambiguously; to this end, additional techniques are required. The advantages of this method include its high throughput, possibility of automation and scaling-up, low reagent consumption, and environmental friendliness (no solvents are required).

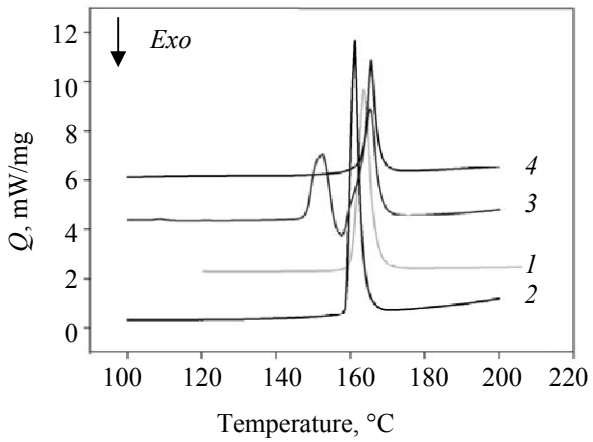

Fig. 6. DSC curves of individual component and their physical mixture and cocrystal: (*1*) A; (*2*) B; (*3*) A : B (1 : 1) cocrystal; (*4*) A + B (physical mixture).

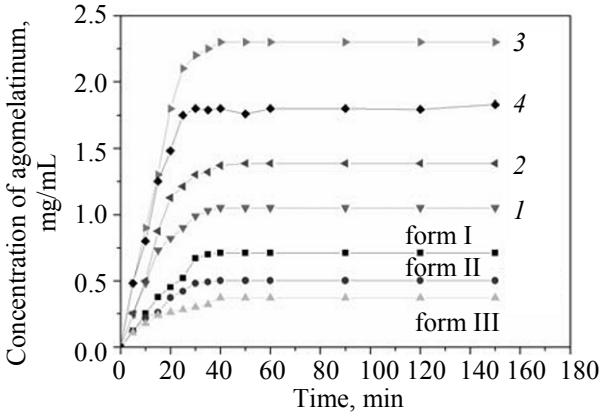

Fig. 7. Kinetic solubility curves of agomelatinum in cocrystals with (*1*) urea, (*2*) glycolic acid, (*3*) isonicotinamide, (*4*) 4-hydroxybenzoate, and (form I–form III) polymorphous of the individual compound in a buffer solution (pH = 6.8).

Table 2. Results of blood analysis after administration of individual PDE4 and a PDE4–tartaric acid cocrystal [51]

Compound	AUC[a], mg mL^{-1} h^{-1}	C_{max}[b], mg/mL
Cocrystal (3 mg/kg)	5.5 ± 4.3	0.44 ± 0.21
PDE4 (3 mg/kg)	0.24 ± 0.9	0.03 ± 0.009

[a] Standard errors are given. [b] The dose was determined by the API.

Other cocrystal screening algoriths are known, and, therewith, some pharmaceutical companies have developed their own algorithms and try not to discover them.

Depending on the rate of screening and the available quantity of the substance to be tested, screening schemes can combine different numbers of procedures (multistep algorithms). The principal idea is to synthesize a sample (candidate cocrystal) and then to estimate any of its properties/parameters to find out whether it differs from those of the individual components. If such difference is detected, the system is selected for further analysis.

Characteristics of Pharmaceutical Cocrystals

The key criterion for choice of pharmaceutical cocrystals on screening is their solubility in solutions mimicking biological media (as a rule, aqueous buffer solutions), since the solubility predetermines the bioavailability of drugs and, as rule, their therapeutic doses.

Let us consider some examples of the solubility of cocrystals with APIs in comparison with the solubility of the APIs in the individual state. Samsodien [48] compared the aqueous solubilities of nevirapine (antiAIDS drug) and its cocrystals with saccharin and tartaric acid. The solubility of nevirapin in water is 0.1 mg/mL, while those of the nevirapin + saccharin and nevirapin + tartaric acid cocrystals are 4.6 and 1.6 mg/mL, respectively. Thus, the solubility of the API in the first cocrystal is 46 times higher and in the second, 16 times higher compared to the individual API.

Yan et al. [49] considered the solubilities of the antidepressant agomelatine in cocrystals with urea, glycolic acid, isonicotinamide, and 4-hydroxybenzoate in comparison with the solubilities of the polymorphous forms of the API (Fig. 7). The maximum solubility enhancement (8 times) was observed in the cocrystal with isonicotinamide.

Let us analyze the advantages of the cocrystal technology, which ensures solubility enhancement, over the synthesis of unstable polymorphous forms. To this end, let us compare the relative solubilities of stable and unstable polymorphous modifications and the relative solubilities of APIs in a cocrystal and in the individual state. Figure 8a shows the solubility ratios of unstable and stable polymorphous forms for 81 compounds [50]. The solubility ratios for eighty polymorphous forms (98.8% of compounds) vary between 1 and 5, and only one compound (1.2%) has the solubility ratio higher than 5.

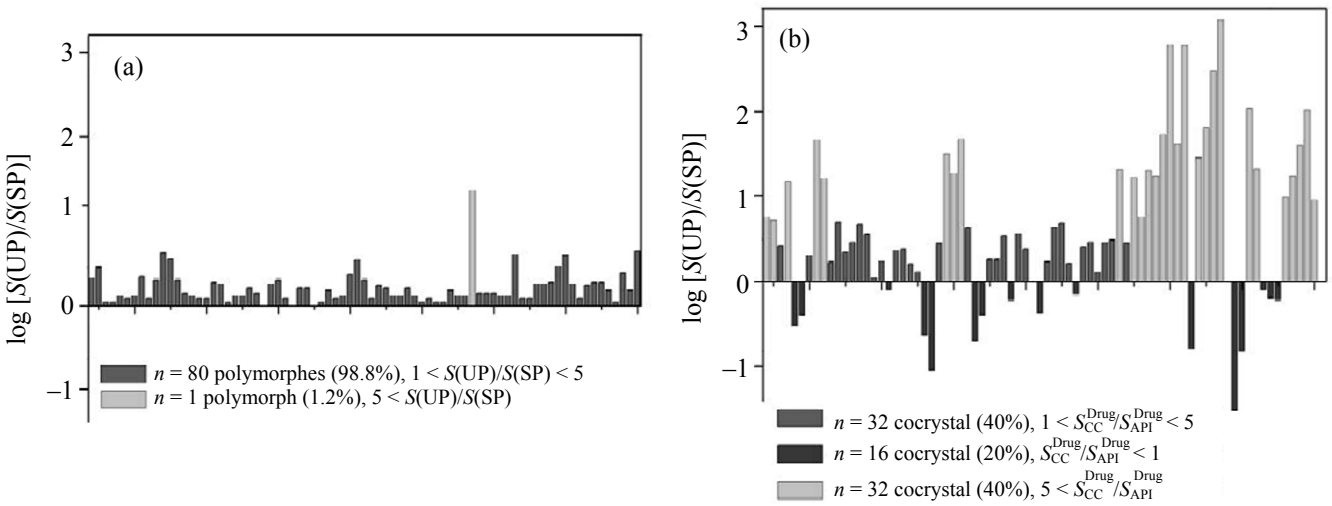

Fig. 8. Solubility ratios of (a) unstable S(UP) and stable S(SP) polymorphous forms for 81 compounds [50] and (b) active pharmaceutical ingredients in cocrystal (S_{CC}^{Drug}) and in the individual state (S_{API}^{Drug}) for 80 cocrystals.

Comparison of the solubilities of APIs in cocrystal and in the individual state (80 cocrystals, Fig. 8b) shows that for 32 cocrystals (40% of analyzed objects, light columns) the solubility ratio falls in the range 1–5, whereas for polymorphous form it is almost 99%. For 32 cocrystals (40%, gray columns) the solubility ratio is higher than 5 against 1% for polymorphs. Thus, the advantage of the cocrystal technology is obvious. Moreover, it should be noted that the solubility enhancement of more than 10 times is attained for 31% of the cocrystals under consideration, of more than 100 times for 8%, and of more than 630 times for 4% of cocrystals.

In conclusion we would like to present parameters which reflect the bioavailability enhancement of cocrystals compared to the individual compounds [51]. The object for study was phosphodiesterase 4 (PDE4), an enzyme that hydrolyzes the phosphoester bond, which is used to treat asthma and chronic obstructive lung disease; the conformer was tartaric acid.

Table 2 lists the AUC (the area under the curve of the time dependence of the PDE4 blood concentration) and C_{max} values (the maximum PDE4 blood concentration) for the individual compound and its cocrystal with tartaric acid (1 : 2), as measured in monkey blood samples after oral administration of the compounds. The AUC and C_{max} for the cocrystal are higher than for the individual compound are 23 and 14.7 times, respectively.

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