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Co-crystallisation as a powerful solubilization approach for Biopharmaceutical Classification System Class II drugs

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Abstract

In accordance with the Biopharmaceutical Classification System (BCS), drugs that fall into Class II are distinguished by having a lower solubility and a higher permeability. Therefore, co-crystallisation has been developed for the purpose of dissolving medications that are notoriously difficult to dissolve. Active pharmaceutical ingredients (API) and coformers are the components that go into the production of co-crystals. Pharmaceutical co-crystals are a type of nonionic complex that can be utilised to solve a range of physicochemical issues, such as solubility, stability, and bioavailability. An item is said to be a co-crystal if it is comprised of two or more different molecular units and is kept together by weak intermolecular interactions such as hydrogen bonding, super-porous systems, and biodegradable hydrogel systems. Co-crystallisation is frequently considered the most efficient method for improving the quality of medications since it can change the molecular interactions and chemical make-up of medicinal substances. Co-crystals provide an alternative approach for API, regardless of whether the API comprises acidic, basic, or ionizable groups. The reintroduction of compounds that have restricted pharmacological properties due to the fact that their functional groups are not ionizable acts as a complementary approach to approaches that have already been established. Inclusion, preparation, and characterization of the co-crystals, as well as several applied research studies, are all topics that are covered in this review, along with their significance in the recent trend towards improving various physicochemical features of BCS class II medications, such as solubilization, stability, and bioequivalence.

Keywords: co-crystal, soluibility, BCS II, poorly soluble.

1.Introduction

Multiple factors influence the efficacy of medicine. The API's physicochemical properties are one of them. The BCS classifies the solubility and permeability of various pharmaceuticals. The BCS categorises medications based on their permeability and solubility, as shown in Figure 1. These points are crucial because the overwhelming majority of medicines sold around the world are intended for oral consumption. Sixty to seventy percent of the recently discovered novel pharmacological compounds are BCS Class II or Class IV compounds, which have reduced solubility and permeability [1, 2].

Co-crystals are multicomponent crystalline systems formed of ordered proportions of distinct molecular and/or ionic components. To enhance the bioavailability, mechanical characteristics, and solubility of previously insoluble solid medications, scientists have turned to co-crystals [3, 4]. Co-crystals consist of two distinct parts. The API and the coformer make up the two halves of the system. The vast majority of coformers are used in the medical industry as excipients, although some of them also have uses as active pharmaceutical compounds [5]. Coformers also include food additives and preservatives of various kinds. Crystals that are generated from APIs are known as co-crystals [6]. The ideal coformer would be a very small organic acid that could make hydrogen bonds with the API. The coformers of carboxylic acid, amide, and alcohol are encountered frequently. Interactions between these functional groups are prevalent in co-crystal systems [7, 8].

Medications belonging to BCS Class II that are poorly soluble in water but have high levels of permeability [9, 10]. Enhancing a medication's solubility can be accomplished employing hydrotropic, complexation, solid dispersion, salt formation, emulsification, co-crystallisation, and nanocrystal methodologies [11]. The solubility of the medicine and its bioavailability are both improved by inclusion complexation. Cavity structures are characteristic of inclusion complexes, which are formed when one chemical (the host molecule) encircles another. The cavity of the host molecule is occupied by a ringed component known as a guest compound [12].

In this article, we discussed the solubility of BCS Class II medications as well as the role of co-crystallisation in overcoming this undesirable feature of this category. In addition, co-crystallisation, synthesis, and evaluation were discussed in considerable depth (Figure 2). Finally, the application of the co-crystal approach to BCS class II was covered, and some recent studies that confirmed an increase in the solubility of co-crystallised forms of these medications were reviewed.

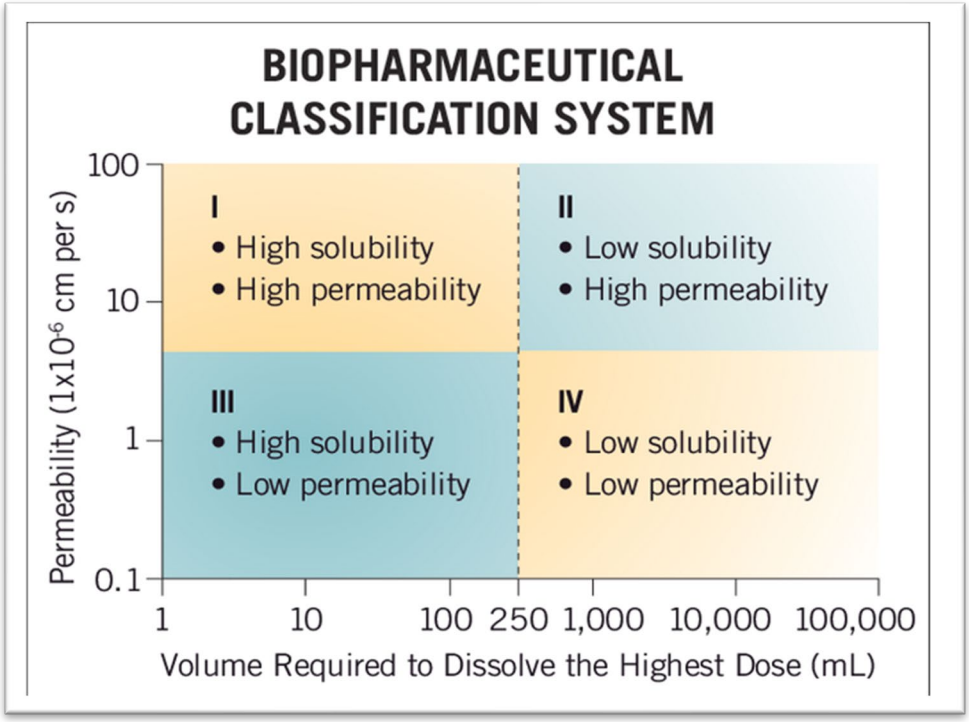

Figure 1: BCS classes of drugs adapted from (Rajadhyax A, Shinde U, Desai H, Mane S. Hot melt extrusion in engineering of drug cocrystals: a review. Asian Journal of Pharmaceutical and Clinical Research. 2021; 14(8): 10-19).

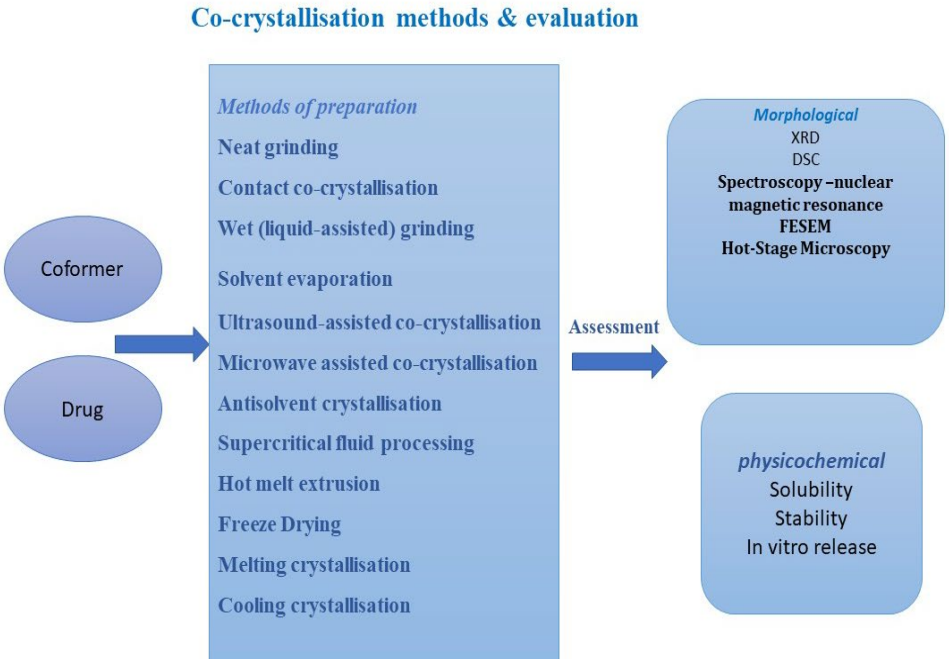

Figure 1: co-crystallisation methods and evaluation

2 .1 Statistical Analysis

2. Co-crystal preparation methods

2.1. Neat grinding

This particular method of grinding creates co-crystals by mixing APIs and coformers while the mixture is subjected to pressure. Blend in a mortar or in a vibrating or ball mill. Controlling the temperature and the amount of time spent mixing can help generate the best possible result. Grinding lasts 30–60 minutes. This method eliminates stability problems by omitting the use of solvents [3].

2.2. Contact co-crystallisation

With the "soft" mixing of raw materials, API-coformer interactions spontaneously occurred [13]. Vapour diffusion of them, moisture sorption, amorphization, and long-range anisotropic molecular motion may explain spontaneous crystallisation by contact [14]. MacFhionnghaile et al. (2020) found that premilling of API and conformer at room temperature and 30% relative humidity produced caffeine-urea co-crystals in three days. They found that caffeine-urea co-crystals formed due to solids' interparticle surface interaction [15]. Moreover, an additional example of spontaneous crystallisation is the isoniazid and benzoic acid co-crystallisation, which showed that moisture promoted the co-crystals' reordering [16]. Premilling the co-crystal physical mixture lowered the nucleation induction time and boosted the composition. Nartowski et al. (2016) showed that moisture addition altered spontaneous co-crystal formation kinetics [17].

2.3. Wet (liquid-assisted) grinding

Solid powders are first catalysed using a variety of solvents, including water, ethanol, and toluene. Only a few drops of the solvent are required. Co-crystal formation can be improved by using a grinding method called solvent drop grinding [18], which binds rather than dissolves the solid particles. This approach results in a co-crystal that has a higher purity than other methods while also being simple, efficient, environmentally friendly, and economical. Wet grinding typically results in higher yields [19].

2.4. Solvent evaporation

This is the most important solvent-based method, including dissolving the API and the coformer in the solvent in order to produce co-crystals [20]. The co-crystal will develop once the solvent has been completely evaporated. While rapid evaporation produces a large number of little co-crystals, slow evaporation results in a smaller number of larger ones. The method of creating co-crystals that is the most reliable is the one in which the solvent is evaporated. In this technique, the drug and the coformer are mixed together in the appropriate proportions before being dissolved in a solvent. When a solvent is allowed to evaporate at room temperature, the result is the formation of co-crystals. It is possible to identify a shared solvent by considering the degree to which the drug and the coformer are soluble in the candidate solvent [21]. The bonding between drugs and coformer functional groups results in the formation of co-crystals. The researchers, Mounika and colleagues, used a variety of techniques to synthesise fexofenadine-tartaric acid co-crystals. Mounika et al. (2015) discovered that solvent evaporation is an easy process that increases the medication's stability as well as its solubility [22]. For example, a 1:1 co-crystal of febuxostat and piroxicam that works through a carboxylic group was made by letting acetonitrile slowly evaporate without heat over the course of three to five days. This co-crystal was more soluble and easier to tablet than its individual components [23].

2.5. Ultrasound-assisted co-crystallisation

In order to manufacture co-crystals, this cutting-edge technique makes use of ultrasonic vibrations, which boost nucleation in solution and speed up phase change processes [24]. A solid ultrasonic probe with a temperature controller and a vessel that can be used with the sonicator where the ultrasonic was utilised by Aher et al. (2010) in order to bring about the formation of caffeine-maleic acid co-crystals. This procedure leads to the formation of a co-crystal that is composed of equal parts caffeine and maleic acid [25]. In a glass vial, the particles will first be solubilized in the solvent. Next, the vial will be sonicated at a controlled temperature until the solution is clear. Finally, the co-crystal will be collected by filtering the solution [26]. Rodrigues et al. (2020) made use of ultrasonic baths in order to facilitate the creation of hydrochlorothiazide co-crystals with a range of coformers [27].

2.6. Microwave-assisted co-crystallisation:

By interacting with the revolving dipoles that make up a molecule, microwave radiation stimulates the molecules and makes it easier for them to move about. The heat from the radiation keeps the solvent in a supersaturated state and guarantees that it evaporates quickly [28]. Co-crystallisation is a

process that can be carried out using either microwaves found in the home or microwave reactors. In contrast to their domestic counterparts, microwave reactors are capable of accurately controlling both power and pressure [29]. After the APIs and coformer have been solubilized in a solvent based on their solubility behaviours, the mixture is transferred to glass tubes and then microwaved at the appropriate temperature, time, and power. A co-crystal is produced when the solution is filtered [29].

2.7. Antisolvent crystallisation

Antisolvent crystallisation is an additional method that can be utilised for the production of co-crystals of superior quality [30]. During this step of the process, a second liquid is added to the medium containing the drug and coformer. This step produces supersaturation. In order for the co-crystal to precipitate, the additional liquid that is being used must be miscible with the solvent [31].

2.8. Supercritical fluid processing

Because of its ability to permeate solids, carbon dioxide (CO2) is the supercritical fluid that is used most frequently in the manufacturing of co-crystals. After dissolving the medication and the coformer in carbon dioxide, they are placed in a tank made of stainless steel. The formation of co-crystals is the end result of a rapid expansion of CO2 due to a gradual decrease in pressure. The drug and the coformer are only partially soluble in the supercritical fluid, which is the primary drawback of this method. Additionally, the clarity of the co-crystals is diminished due to this method [20].

2.9. Hot melt extrusion

It is a process in which a drug is embedded in a melted polymeric matrix with the required characteristics to modify solubility and stability. Thermolabile compounds could be handled at a lower temperature to avoid degradation [24]. Hot melt extrusion may be the best option for the continuous manufacturing of co-crystals, where co-crystals are produced by heating the drug and coformer to a miscible state and then vigorously mixing them together in an extruder [32].

2.10. Freeze Drying

Freeze drying, also known as lyophilization, is another method that could be utilised in the manufacturing of pharmaceutical co-crystals. During the process of freeze drying, moisture is extracted from

a substance by first freezing it, then allowing the ice to sublimate straight to vapour at a low partial pressure of water vapour. This removes the moisture from the substance. This is a process that consists of multiple steps that are utilised in food and pharmaceuticals for the goal of preserving products, and this technology is applied in those fields. In more recent times, it has been demonstrated that this method can be effectively utilised to prepare novel solid forms of co-crystal systems [33, 3].

2.11. Melting crystallisation

Melting crystallisation can make pharmaceutical co-crystals greener. Despite the fact that no solvents are employed in this method, the stability of the drug and coformer should be assessed. Melatonin-pimelic acid co-crystals were melted and crystallised by Yan et al. (2015) [34]. Melatonin-pimelic acid co-crystals were formed in the liquid at temperatures between 50 and 70 degrees Celsius. To create the carbamazepine-nicotinamide co-crystal, the drug-coformer mixture was melted at 160 °C before being cooled to room temperature for crystal development, which resulted in a crystal structure with a nicotinamide atom [35]. The crystallisation mechanisms of the carbamazepine-nicotinamide from the melt after heating were studied, and the carbamazepine-nicotinamide co-crystal nucleated in a metastable phase and transitioned to the stable form at a slow heating rate (3 °C/min), while at a rate of 10 °C/min, the constituent parts of the co-crystal crystallised separately, were melted, and the stable form grew from the melt [35].

2.12. Cooling crystallization

The cooling crystallisation method is widely utilised for the production of large, pure co-crystals. The distribution size, purity, shape, and polymorphism of these co-crystals are dependent on the localised supersaturation [36]. During the process of crystallisation, the operational region is established according to the stoichiometry of the co-crystal as well as the thermodynamic stabilisation region at both the starting temperature and the finishing temperature. Many investigations have shown that this method is an effective one for increasing the production of co-crystals on a larger scale. These co-crystals had a purity level of 99% and were of uniform particle size. In order to initiate the nucleation of the co-crystals, a seeding slurry with a weight-to-volume ratio of 10% was injected into the crystallizer at a temperature of 10 degrees Celsius for ten seconds [37].

3. Assessment of the co-crystals

3.1. Characterization

3.1.1 X-ray (XRD) investigations

Co-crystal unit cells can be phased using this analytical tool. Crystallography, both single and powder X-rays, has the potential to show co-crystal formations. XRD is utilised to identify co-crystals by detecting differences in the crystal lattice. Crystal sourcing is the primary challenge faced by single-crystal XRD [38].

3.1.2. Differential scanning calorimetry (DSC).

Pharmaceutical co-crystals are usually characterised using the DSC. This method involves heating co-crystals and pure components at a predetermined rate and evaluating the thermogram to determine if co-crystal formation occurred [39]. The eutectic melt generated at mild heating rates recrystallizes to the co-crystal form before melting, regardless of the drug-to-coformer ratio. A DSC-scan thermogram can detect co-crystals. Co-crystal thermograms show an exothermic peak, unlike medications and coformers. Then comes an endothermic peak. It's likely that co-crystal melting and fusion temperatures will vary. Due to physical combinations that cannot form co-crystals, thermograms show just one endothermic peak during eutectic melting [40].

3.1.3. Spectroscopy: vibrational, nuclear magnetic resonance

In spectroscopy methods, also known as infrared and Raman spectroscopy, the chemical bonds in co-crystals absorb or scatter energy in a manner that is distinct from that of pure substances; this shows the structural behaviour of the co-crystals. Due to the hydrogen bonding presence, the infrared spectra of co-crystals are distinguishable from those of the pure drug and the coformer. Bands of hydrogen-bonded functional groups are distinct from one another. A neutral carboxylic acid group (COOH) has a stronger tension band of C=O at approximately 1700 cm-1 and a lower tension band of C=O at approximately 1200 cm-1, respectively, and a carboxylic anion (COO) has a weak tension band between 1000 and 1400 cm-1 as a result of salt production. Both of these tension bands are caused by the C=O bond. The OH....N H-bonding process produces two significant zones, one at 2450 cm-1 and another at 1950 cm-1. Solid-state nuclear magnetic resonance is used to characterise co-crystals

since it can provide information regarding the structures of the co-crystals [41]. This method differentiates between co-crystals and salts by measuring the transit of protons, which is a characteristic of co-crystals. One disadvantage of this method is that the instrument sensitivity is quite low [42].

3.1.4. Field emission scanning electron microscopy (FESEM)

The topography of co-crystals can be investigated using FESEM. Examining the similarities and differences between FESEM components and co-crystal micrographs. The energy utilised by the field emission electron microscope can be described as "cold." Strong electric fields cause the conductor to release electrons into the surrounding space. In cathodes (10–100 nm), tungsten filaments with extremely fine needles are utilized. Both the field emission source and the scanning electron microscope are used to take the micrographs of the co-crystals [43].

3.1.5. Hot-Stage Microscopy

Microscopy and temperature analysis are both utilised in hot-stage microscopy. The physicochemical characteristics of a substance are affected both by temperature and by the passage of time. Under a microscope, it is possible to observe the melting point, melting range, and crystalline transition of a co-crystal sample that has been preserved on a glass slide [44].

4. Physicochemical investigations

4.1. Solubility test

After placing the co-crystal sample and the media in an Erlenmeyer flask or another container of the appropriate size, the mixture is shaken for twenty-four hours in a rotary flask shaker. After 24 hours, the material is subsequently filtered, diluted, and subjected to HPLC analysis [45]. Using the co-crystals approach in conjunction with n-acetylcysteine as a coformer, Paulazzi and colleagues were able to enhance the bioavailability of curcumin [46].

4.2. Stability

Examining how co-crystals and pure active compounds fare in terms of their stability and shelf life 40 degrees Celsius with 75% relative humidity is the standard temperature and humidity utilised [47], while 25 degrees Celsius with 60% relative humidity is the standard for 1, 3, or 6 months [48], evaluating the co-crystal's stability in contrast to the pure API's and its shelf life [49].

4.3. In vitro dissolution:

The formulation's in vivo performance can be predicted based on the release, which can also be employed to measure the percent of medication that accumulates over time. Studies of the co-crystals' release are carried out with the assistance of the dissolving equipment. The co-crystal dissolution research is carried out at various points across the permitted dissolution medium, as outlined in the medication protocol for the mentioned assembly [49]. The samples are collected in the appropriate volumes at the predetermined measure, and they could then be analysed using appropriate methods such as [50].

5. Examples of drugs whose bioavailability is enhanced by co-crystallisation

BCS Class II drugs include many drugs that are required to have rapid action for life-saving purposes, such as antidiabetics and antihypertensives. Recent publications include the results of some experiments that were performed to affect the physical properties of BCS class II medications by using co-crystallisation.

5.1. Antidiabetcs

Many antidiabetic drugs have the property of poor solubility. As a result, improving their solubilization is critical for saving lives. For instance, Srivastava et al. were able to solubilize glibenclamide (GLB) by employing coformer malonic acid, thanks to the assistance of co-crystallization. The co-crystal was subjected to solubility and release tests, as well as DSC, PXRD, and IR spectra, all of which validated the formation of the co-crystal. When GLB was co-crystallised, its solubility and dissolution were both increased by a factor of two [51]. Moreover, Gliclazide (GCZ), Tolbutamide (TOL), and Glipizide, BCS Class II antidiabetic medicines lacking water solubilization, were co-crystallised by Samie et al. Liquid-assisted grinding employing coformers like catechol, resorcinol, p-toluenesulfonic acid, and piperazine (PPZ) yielded GCZ multicomponent solid forms and co-crystals. Single crystal, powder, Fourier IR, DSC, thermal gravimetric, and solubility experiments were performed on multicomponent solids. All co-crystals have higher levels of solubility and release than their parent active medicinal ingredients. The solubility of GCZ-PPZ and TOL-PPZ increased by 6.6 and 80 times, respectively [52].

5.2. Antihypertensive

Liquid-assisted grinding and solvent evaporation produced antihypertensive drugs like nebivolol hydrochloride co-crystals, where the parent drug disintegrated much slower than the co-crystals. Nikam & Patil (2020) blend 4-hydroxybenzoic acid and nicotinamide (NA) to make BCS class II antihypertensive nebivolol hydrochloride co-crystals [53]. AMT is licenced to treat pulmonary arterial hypertension. AMT is a BCS II molecule since it is only 0.06 mg/mL in water. Ambrisentan (AMT) and glycylglycine co-crystals develop via hydrogen bonding, and the co-crystal has a higher bioavailability than pure AMT [54].

5.3. Antihistaminics

Setyawan et al. (2021) generated a loratadine-succinic acid co-crystal by employing succinic acid as the conformer. This was accomplished through the application of the solution approach, which involved the use of methanol. The presence of an intermolecular hydrogen link between loratadine and succinic acid may be seen in IR spectra. In the co-crystal phase, the solubility of loratadine was enhanced by interactions between C=O and H-O, resulting in a 1:1 loratadine-succinic acid co-crystal [55].

5.4. Erection - extending enhancers

This category is not for lifesaving, but it is important for a good quality of life, especially for men with problems with erection. Shimpi and colleagues (2018) co-crystallised tadalafil (TDF) with malonic acid (MOA) to increase the drug's solubility. The crystalline structure revealed that the TDF molecules formed hydrogen bonds, indicating that the stoichiometry was 1:1 for the compound, which demonstrates an increase in the rate of disintegration [56].

5.5. Anthelmintics

Yang et al. (2022) solubilize praziquantal by using solvent-assisted grinding (SAG) and solution slow evaporation (SSE). In this particular research, SAG and SSE were used in order to synthesise five different co-crystals of praziquantel (PRA) with polyhydroxyphenolic acids. Co-crystals of PRA-phenolic acids generated by SAG and SSE and their solubility and bioavailability were investigated and found to be increased [57].

5.6. Anticholestremia

Nanda, A., and Anand, R. (2022) increased the solubility and dissolution of a BCS-class II (Ezetimibe) drug by using co-crystallization with glycine as a coformer and by modifying the chemical structure of the drug. In 90 minutes, co-crystals were able to spread and dissolve more quickly than pure drugs [58].

5.7. Antibiotics

Surampudi et al. (2023) developed BCS class II anti-folate trimethoprim (TMP) co-crystals by using the coformers theophylline-7-acetic acid (T7A), 5-fluorouracil, catechol, and thymine. The system that includes the aminopyrimidinium-carboxylate synthon, which is represented by the notation TMP-T7A, has the highest level of solubility [59].

5. Conclusion

As a result of the poor solubility of BCS Class II pharmaceuticals, the process of developing a wide variety of medications has become significantly more difficult. Therefore, increasing their solubility will result in a rise in their bioavailability. According to the findings of this review, the process of co-crystallisation has a considerable impact on both the solubility and the bioavailability of BSC Class II medications. Co-crystallisation alters qualities such as solubility, release rate, and chemical and physical stability, resulting in substances having higher-level attributes than those of the pure drug. This review offers a detailed discussion of techniques, cofomers, characterization, and evaluation, as well as many drugs that benefited from co-crystallisation with appropriate coformers and their results, especially lifesaving drugs.

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