Pharmaceutical cocrystal and their role in improving solid state properties of active pharmaceutical ingredients

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Abstract:

Cocrystallization is an emerging approach for improving physico-chemical characteristics of an active pharmaceutical ingredient (API) for instance dissolution rate, solubility, stability in addition to mechanical properties without affecting their therapeutic activity. It is of great importance when other approaches like salt or polymorph formation do not encounter the estimated targets.

In this review article, an outline of pharmaceutical cocrystals will be presented, with highlighting on factors affecting cocrystallization which include ΔpKa, donors and acceptors hydrogen bonds, molecular recognition point, synthon forming functional groups flexibility, dicarboxylic acid coformers carbon chain length and solvent effect, as well as and the methods for cocrystal preparation. Additionally, cocrystal characterization, dissolution pattern as well as the commercially available products were discussed.

Key words: Cocrystal, dissolution rate, solubility.

المشارك المتبلور ودوره في تحسين خصائص الحالة الصلبة للمواد الصيدلانية الفعالة

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الخلاصة:

تصييغ المشارك المتبلورهو نهج ناشئ لتحسين الخصائص الفيزيائية والكيميائية للمادة الصيدلانية الفعالة كمعدل الذوبان و الاستقرار بالاضافة الى الخواص الميكانيكية دون التأثير على نشاطها العلاجي. ويعد ذا أهمية كبيرة عندما لاتحقق الطرق الاخرى الاهداف المقررة كتكوين الملح او تكوين متعدد الاشكال.

في مقال المراجعة هذا سيتم تقديم الخطوط العامة للمشارك المتبلور الصيدلاني, مع تسليط الضوء على تصييغ المشارك المتبلور و طرق تحضيره و مناقشة توصيفه و نمط الذوبان وكذلك المنتجات المتاحة تجارياً للمشارك المتبلور.

الكلمات المفتاحية: المشارك المتبلور,معدل الذوبان ,الذوبانية.

Introduction

Attributable to point that about 40% of permitted drugs and almost 90% of drugs in developmental stage exhibit poor water solubility which is mainly because of an increased in molecular weight and lipophilicity. The furthermost significant concern from the pharmaceutical then

pharmacological standpoint is to improve drug solubility [1,2]. Such problems have encouraged scientists to follow other ways of developing pharmaceutical produces, for instance through discovering innovative forms of solid state of APIs from the old one by means of salt formation or else co-crystallization procedure, consequently modifying final characteristics deprived of alteration in the pharmacological activity[3].

Historically, the first choice to overcome problems associated with low solubility and slow rate of dissolution, has long been salts formation while in recent times, cocrystals have been the focus of emerging research[4]. Aimed at pharmaceutical/ chemical improvement in addition to pre formulation phase aspects, it is important to understand the essential difference among salt formation and cocrystals. Salt formation involve the creation of system containing three components; an acid, a base as well as single or multiple solvents. The proton (H^+) transference as of an acid toward a base give rise to salt [5].For cocrystal, since both API as well as cocrystal former are exist in form of crystal lattice, there is no proton (H^+) transfer. Therefore, for dugs with ionizable functional groups, the simplest method to improve drug properties is salt formation. Unlike salts, cocrystals are excellent alternate for non-ionizable drugs [6].

The earliest cocrystal can be outlined back to 1844 with Friedrich Wöhler and the discovery of quinhydrone, throughout the study of quinones. Its complete molecular structure in addition to intermolecular interactions were published for the first time in 1958 (due to the absence of X-ray analysis at that time) [7] .

In this manuscript, different features of cocrystallization technology were discussed like advantages and limitation, factors determining cocrystallization, synthesis and characterization techniques, dissolution pattern of cocrystals and commercially available cocrystals.

Definition

Cocrystals are distinct as “solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts” [8]. Hydrogen bindings (the main interaction), van der Waals forces as well as π-π interactions, which are noncovalent interactions are responsible for the development of cocrystals [9]. When the co crystal results from the conjugation an API with a pharmaceutically accepted excipient (known as co former), the resultant compound is known as pharmaceutical cocrystal [10] and as shown in Figure 1.

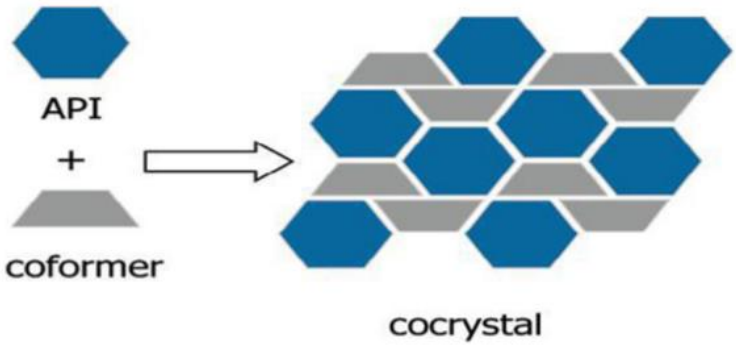

Figure (1): Cocrystal multicomponent system [11]

Advantages and limitation of cocrystals

Owing to their advantages, cocrystals have become progressively widespread drug modifications. The main advantage is the opportunity to enhance the solubility and stability of poorly soluble neutral APIs [12]. Additional valuable advantages include: The possibility of preparations of numerous cocrystals for each drug due to the availability of various counter molecule (coformers) [13] , possibility of discovering wide range of new API forms since they can be made for both ionizable and non-ionizable drugs molecules , modification / improvement of both mechanical and pharmaceutical properties as well as possible extension of old APIs life cycle by cocrystal formation [14, 15] .

Basically, cocrystals controlling the physicochemical properties of APIs by means of addition of an appropriate coforemer. Consequently, it is important to consider and not to ignore that coformers should be safe, accepted pharmaceutically, cheap, and provide strong intermolecular binding, with multiple binding site with API and low molecular weight. The addition of coformer will resulted in larger dosage forms which cannot be overcome particularly when the drug dose is on gram scale, another concern is related to large scale cocrystal production [16].

Factors Determining Cocrystallization

ΔpKa Rule

To assess the ability of cocrystal development of a coformer using a specified API , the difference between pKa (dissociation constant negative logarithm) value of API and coformer (ΔpKa) value has been used [17]. pKa value specifies the capability of an acid molecule to transfer a proton (H^+). Negative values of ΔpKa indicate no proton transfer [18]. As a result, one can probably assume no cocrystal formation in such circumstances [19]. On the contrary, when the value of ΔpKa is more than 3 of proton transference is accomplished and, salt formation is detected [17-19]. Berry and Steed suggested that, salts are formed once ΔpKa value exists adjacent to that of a base, and cocrystal is formed when it remains close to the acid [18]. An experimental analysis is essential for accurateness since prediction /conformation of a solid phase in all circumstances cannot be always done using ΔpKa value. Da Silva et al. designed as well as developed 5-Fluorocytosine cocrystals by using different co formers [20]. The formed solids were referred to as salt-cocrystal, the ΔpK avalue ranges between 0 and 3 [17, 21]. Interestingly, salt formation was identified in an attempt to develop clotrimazole cocrystals by Nangia et al using some carboxylic acid coformers , for the system ΔpKa value was 0.93 [21, 22].

Donors and Acceptors Hydrogen Bonds

The extent of success in a cocrystals formation is also determined by coformer and drug molecules donors in addition to acceptors number of hydrogen bond. Cocrystals are probably formed by coformer molecules with molecules that are able to offer numerous hydrogen bonds [23].

Hydrogen Bond Rules was outlined by Etter [24] and Donohue [25] to anticipate the conditions under that hydrogen bond interactions which resulted in cocrystals [24, 25]. These rules are as specified below:

1. In hydrogen bonding, generally all good proton donors (like –NH4+, –COOH,) in addition to acceptors (like –NH3, –OH) are used.
2. Intramolecular hydrogen bonds of six-membered ring (like C-H... O) are established initially in favorite to intermolecular hydrogen links (like O-H... O as well as N-H... O) ,
3. The superlative proton donors as well as acceptors existing after intramolecular hydrogen- bond formation then contribute in intermolecular hydrogen bonds with one another,

4. In the crystal structure, all acidic hydrogen atoms are involved in hydrogen bonding.

Molecular Recognition Points

Molecular recognition measures are in charge for the self-assembly of two or else further components via noncovalent interactions through energetically promising geometries [26].

The selection of the coformer to cocrystallize with API depends on awareness of both geometries as well as ideal orientations of available intermolecular interactions [27].

The molecules of API comprise definite active group (elsewise molecular recognition point) in its structure that networks by means of the coformer and thus produce supramolecular entity which termed as supramolecular synthons [28].

Synthon as a term was presented via Corey for the first time in 1967 who interpreted synthons as "Structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermol-ecular interactions" [29].

These supramolecular synthons are divided into homosynthons and heterosynthons depending on the corresponding active moieties in both, drug plus coformer [30]. Homosynthons are a result from the interaction between similar functional groups (for instance amide...amide and acid...acid groups) while hetro-synthons are resulted from the interaction between dissimilar functional groups (for instance acid...amide, amide...pyridine groups and acid...pyridine groups). Halogen bonding could also produce hetrosynthons. Furthermore, these intermolecular interactions could be homomeric between the similar molecule or heteromeric, between unlike molecules [28].

Synthon Forming Functional Groups Flexibility

Besides molecular recognition points, the functional groups site as well as the participating molecules conformational flexibility show a significant part to determine the success rate of a cocrystallization [31].

An extensive study was carried out by Aakeroy et al. to recognize by what means polymorphic combinations aid as an acceptable coformers, emphasizing on the effect of conformers of synthon functional moieties flexibility throughout whichever cocrystallization. The cocrystal forming capability of polymorphic compounds, 2-amino 3-nitropyridine, isonicotinamide, 4-chlorobenzamide in addition to maleic hydrazide was studied experimentally. The results showed that all the compound except maleic hydrazide exhibited active participation by intermolecular hydrogen bonding through aromatic and aliphatic acids and thus were found to be appropriate candidates for cocrystal-llization. This was attributed to the ability of these compounds to display hydrogen bonds among unlike functional moieties individually of their polymorphs. While every maleic hydrazide polymorphs permanently displayed the primary hydrogen bonds interactions among similar active moieties that reduces the opportunity of development of new-fangled hydrogen bond synthons by further molecules [32].

Dicarboxylic Acid Coformers Carbon Chain Length

One of the most used coformers are carboxylic acids due to their ability to form heterosynthons by active ingredient molecules having pyridine and amide functional moieties besides homosynthons through molecules having acid functional moiety. On the other hand, the length of carbon chain in carboxylic acids will also affect the tendency of cocrystal formation. Shevchenko et al. and during their study to form itraconazole cocrystals by means of aliphatic chain dicarboxylic acids with various length of carbon chains. They noticed that the increase in the length of the coformer carbon chain resulted in

lowering the possibility of geometrical suitability of coformer through to the active ingredient lattice because of steric hindrance of bulky carbon chain to accurately position through to the crystal lattice of active ingredient [33].

Effect of Solvents

The success of cocrystallization process affected significantly by the solubility of both the API besides coformer in a solvent intended for cocrystallization. Identification of cocrystal formation region, comprehended the chemistry of solution in addition to co crystals solubility behavior can be identified by using the Ternary Phase Diagram (API-co former-solvent) [34]. Among the most significant parameters which control the cocrystal formation zone in ternary phase system are the solubility of both API and coformer, solvent system polarity, temperature plus pH. Robertson et al. concluded that due to the effect of polarity of various solvents on the strength of interactions between molecules , less polar solvents favors hydrogen-bonded cocrystals formation while halogen-bonded cocrystals formation was preferred by the more polar solvents [35].

Cocrystals synthesis techniques

Solvent-free methods

Hot melt extrusion

This process involves feeding the raw materials into a rotating screw under controlled temperature. The friction generated between the barrel and the screw of the extruder raises the temperature and causes melting of the blend. This would improve the surface contact among API and coformer lead the way to development of cocrystals deprived of solvents [36].

Hot melt extrusion presents a cost-effective and economic process as it requires lower processing stages when related to other techniques. Besides, the product quality could be optimized through controlling process parameters, for instance temperature, mixing intensity as well as screw features (e.g., configuration, size, type, plus speed). However, it is not suitable for thermally labile drugs due to degradation risks at high temperature conditions [37] .

Mechanochemical grinding

Mechanochemical cocrystallization occurs as a result of a mechanochemical reaction, which is defined by the International Union of Pure and Applied Chemistry (IUPAC) as per a chemical reaction induced by mechanical energy. Applied mechanical stress promotes fracture and increases the exposed surface area leading to interpenetration and reaction between API and coformers [38].

Mechanochemical grinding can be performed either manually by means of mortar or pestle or else mechanically, by ball milling technique. In ball milling method, the materials are fed into a rotating chamber containing ceramic or stainless steel balls [39].

While manual grinding has been associated with scalability and low yield difficulties, ball milling has been reported as a rapid also effective method for cocrystal synthesis. Trask et al. successfully produced six caffeine - dicarboxylic acid cocrystals using ball milling [40]. Heiden et al. effectively produced a cocrystal of theophylline besides benzoic acid. The data obtained from X-ray characterization showed that cocrystals had been formed after 25 minutes of ball milling [41].

Liquid-assisted grinding

In this method, a small quantity of solvent is added during grinding process. The solvent functions as a catalyst which increases the rate of cocrystal formation. Kinetic enhancement might be attributed to the increase in the degree of orientation and conformational freedom of the molecules and molecular collisions [42]. Though solvent addition, this method is considered as a solvent-free method, because the main mechanism of cocrystallization is the mechanochemical energy from grinding. According to the

literature, it appears that this method is more efficient than neat grinding in terms of higher yield, product crystallinity and polymorphs formation selectivity [43].

Many researches demonstrating the formation of carbamazepine- nicotinamide and carbamazepine - saccharine co crystal by means of liquid assisted grinding [44].

Despite the beneficial role provided, liquid assisted grinding has still been used in lab-scale and has limitations correlated to high energy consumption and undesirable solvate formation [45]. Among pharmaceutical co crystals prepared by liquid assisted method are carbamazepine nicotinamide and carbamazepine saccharine

Solvent-based methods

Solvent evaporation technique

In this process, cocrystals are produced as a result of supersaturation caused by removal of the solvent via evaporation. Supersaturation state will lead to the nucleation and crystals growth from a solution of both API and coformers [46]. This technique has been used successfully at laboratory scale as it has proved efficiency in screening of the best coformer-API combination [47]. On the other hand, it has been found difficult to adopt at large scale production, due to the environmental hazards and the possible formation of undesirable solvates instead of cocrystals [48].

Spray drying

Spray drying is a well-established method in controlling particles size and morphology. It has been widely used in pharmaceutical industry prepared as solid dispersions, and nanoparticles. It has also impressive features in terms of the relative ease to scale – up and the optimization of the process variables [49].

Spray drying involves two phases: atomization and drying phases. Even though the definite mechanism of cocrystal establishment is not fully understood, it is assumed that cocrystals may form as a result of fast solvent evaporation as well as solidification of liquid droplets causing a state of supersaturation. Supersaturation will facilitate nucleation and growth of cocrystals between API and the co former [50].

Antisolvent crystallization

The addition of antisolvent into a solution containing drug-coformer mixture will create a state of supersaturation leading to precipitation of cocrystals. The proper selection of the solvent/antisolvent pair is critical in this technique. Antisolvent must be miscible with the solvent, and cocrystals must be sparingly or insoluble in it [51]. Ethanol/acetonitrile, ethanol/water, in addition to ethanol/ethyl acetate are specimens of solvent/anti-solvent mixtures employed in various literature to produce cocrystals [52].

Chun et al. were the first to employ this method in cocrystal synthesis. They used water as antisolvent and methanol as a solvent to produce indomethacin – saccharin cocrystals [52]. It was concluded from various studies that the final product properties as cocrystal size, morphology, polymorphism, purity and yield could be controlled through optimization of variables such as solvent/anti-solvent ratio and drug/coformer ratio [53].

Freeze drying

Freeze drying is a well-established process commonly employed in the formulation of amorphous systems. It has requisition in biotechnology, pharmaceuticals, food in addition to diagnostics industries. Freeze drying consists of two steps: the rapid freezing of a solution subsequently solvent sublimation under reduced pressure. The resultant product consists of a low-density powder, in general in amorphous form. It was found by Eddleston et al. that amorphous form could be transformed into crystals provided that the product's glass transition temperature is below ambient temperature [54].

High shear granulation

A common method in pharmaceutical industry. In this technique, addition of liquid onto agitated powder particles facilitates granulation by formation of capillary as well as viscous forces between particles. When the achieved granules are dried, in a drying step, additional permanent bonds are formed [55]. During these steps, change in crystalline phase can take place as a result of solvent exposure as well as thermal plus mechanical stress. This method had been successfully introduced for the synthesis of piracetam–tartaric acid cocrystals by Rehder et al. The study revealed that several factors determine formation of cocrystals, for instance the exposure time, the volume of granulation liquid, the impeller speed and the coformers used [56].

Supercritical fluid technology (SCF*)*

Gases at temperature and pressure above their critical point, exhibit both properties of gas and liquid serving many pharmaceutical applications. The most commonly used supercritical fluids are carbon dioxide and water. SCFs have been recognized as green solvents, with a high solvation power and tunable fluid properties. Besides, the technology offers advantages of being a scalable method that produces cocrystals in a single step. It also requires moderate temperatures making it a suitable method for thermally sensitive substances [57]. Supercritical CO_2 has three different roles in cocrystals synthesis [58]. Consequently, three techniques have been applied: firstly, cocrystallization thru supercritical solvent, is depend on the SCF solvent power; where pure components are dissolved in supercritical CO_2, the depressurization causes supersaturation and cocrystals formation. Secondly, supercritical anti solvent, based on the anti-solvent effect where components are dissolved in organic solvent but insoluble in SCF. Finally, atomization and anti-solvent. In this process, a solution containing the API and coformer is pumped through a nozzle into a mixing chamber where it is mixed with the supercritical CO_2 or N_2. SCFs are able to split up liquid solutions in smaller droplets on depressurization leading eventually to cocrystals precipitation [59]. SCF were employed by Courtney *et al* and Abhijat *et al* to develop carbamazepine - nicotinamide as well as itraconazole - succinic acid cocrystals by using pressurized CO2 respectively [60,61].

Characterization of Cocrystals

Characterization of cocrystals mainly involves structural analysis , spectroscopic analysis, thermal analysis, microscopy and drug release testing [14].

Structural analysis refers to studying the crystalline identity of the produced solid phase using techniques as powder x-ray diffraction (PXRD) and single crystal x-ray diffraction (SCXRD). The formation of a new crystalline state is verified through the appearance of diverse characteristic peaks when related to the spectra of API and the coformer. PXRD lay out information regarding the solid crystallinity [62]. SCXRD is used to discover the structure of cocrystals at the atomic level (e.g., unit-cell dimensions also crystallographic space groups). It correspondingly provides comprehensive three-dimensional positioning, sites of atoms in addition to packing of molecules in the unit cell. Therefore, supramolecular synthons can be interpreted from this three-dimensional arrangement [63].

Spectroscopic procedures like infrared, near-infrared, Raman and terahertz pulsed spectroscopy have been applied in studying the intermolecular interactions. Intermolecular hydrogen bonding is evidenced by means of a shift in stretching bands of moieties to lower frequencies in addition to peak broadening [64].

Intermolecular hydrogen bonding between bicalutamide and sucralose at (1:4) molar ratio Figure 2 has been suggested based on the significant changes in absorption bands in the formulation, when compared to

those of the parent components implying cocrystal formation [65].

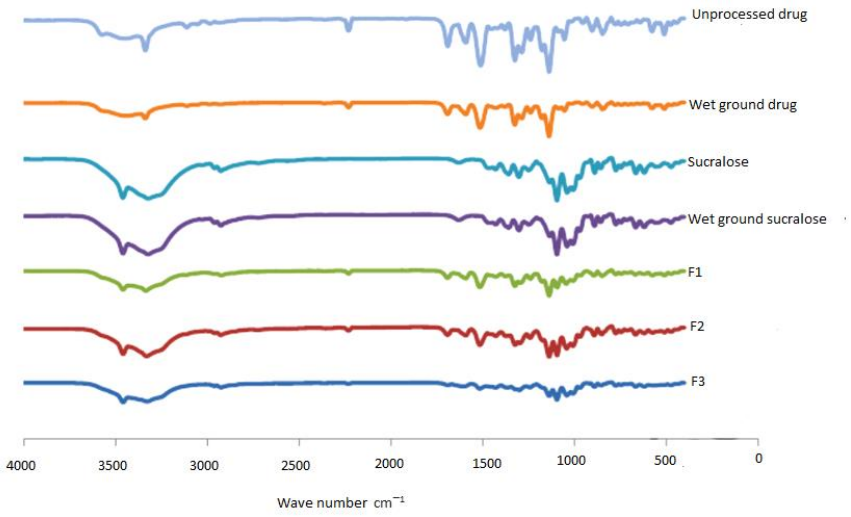

Figure (2): FTIR spectra of pure unprocessed drug, wet ground drug, sucralose, wet ground sucralose, F1, F2, F3 [65].

The production of cocrystals of sulfamethazine with p-aminobenzoic acid (PABA) was investigated via Raman spectroscopy. The spectra of pure sulfamethazine have bands at 1342 cm^{-1} plus 1637 cm^{-1}, assigned to NH deformation and NH_2 bending, correspondingly, while the spectra of the sulfamethazine through PABA product, obtained via solvent drop cogrinding, revealed a shift of bands to 1359cm^{-1} and 1627cm^{-1}, as shown in Figure 3. Slight band shifts are attributed to cocrystal formation, since larger shift of 30 to 40 cm^{-1} are anticipated in the situation of a salt. In addition, the rise in the NH deformation frequency from 1342 cm^{-1} to 1359 cm^{-1} implies that the sulfa NH is involved in the hydrogen bonding [66].

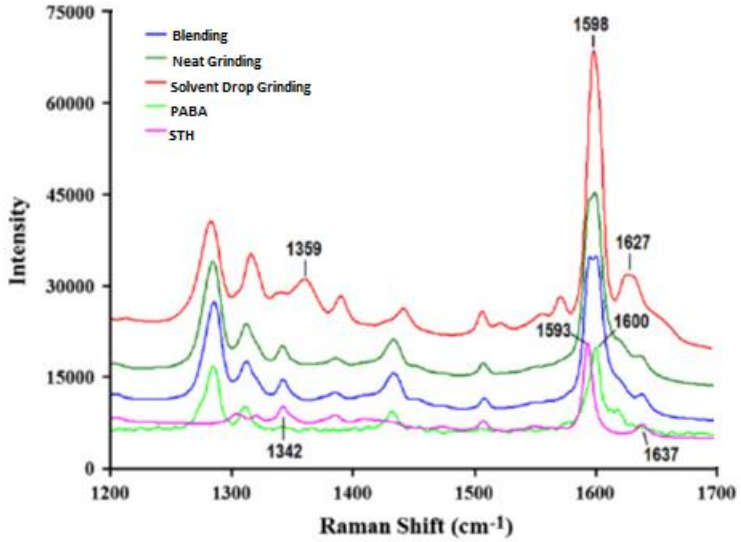

Figure (3): Raman spectra in the region from 1200 to1700cm^{-1} of sulfamethazine with p-aminobenzoic acid (PABA) mixtures after blending, neat cogrinding and solvent-drop cogrinding [66].

Solid-state nuclear magnetic resonance (SSNMR) is a complementary to X ray diffraction, or even an alternative approach as it provides information about crystal structure in samples with poor quality to be characterized SCXRD [67].It is a multinuclear methodology due to its capability to probe each carbon, nitrogen or even directly the hydrogen atoms ,it provides data on the existence in addition to hydrogen bonds strength and the proton transfer from the acid to the base with development of charge-aided contacts [68].

A nuclear magnetic resonance spectroscopy that could be intended for verifying stoichiometric ratio of cocrystal phases is known as proton NMR spectroscopy [69].

Thermal methods comprise techniques that measure the alteration in the thermal properties of a sample as a function of temperature change. The most common techniques in the analysis of cocrystals are differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and hot stage microscopy [70].

DSC is a helpful tool for rapid screening of cocrystals during the stage of synthesis. In addition, it has been considered to distinguish cocrystals from other multicomponent mixtures and thereby selecting the best coformer [71].

The DSC curve of a cocrystal usually shows a distinct endotherm by melting point lesser or in between or higher than the melting points of the coformer and API. This state varies with the physical mixture, where two endothermic peaks appear in the DSC thermogram each analogous to the melting point of the specific constituent [72]. A eutectic is expected once the DSC thermogram demonstrate a lower melting endotherm than the melting points of either of the individual components. On the other hand, the absence of a sharp endothermic peak and the appearance of glass transition phase alteration suggests the development of a coamorphous solid dispersion [31].

Hot stage microscopy allows a visual observation of phase transition events, as melting, recrystallization, and dehydration and desolvation, which occur as a function of heating process. Therefore, it is considered a valuable tool in initial screening phase of crystallization process [73].

Dissolution pattern of cocrystals

Dissolution enhancement

Cocrystals, among many approaches such as crystalline salts, amorphous dispersions in polymer matrix, and nanoparticles have been applied to achieve a state of supersaturation of poorly soluble drugs [74].

Cocrystal dissolution profile could be explained by the “spring and parachute model”, shown in Figure 4, in this model, the drug concentration reaches a maximum peak value in a relatively short period of time known as a spring effect. This high concentration is keep up for an extended period , then followed by a decrease toward the level of equilibrium solubility (parachute effect) [30].

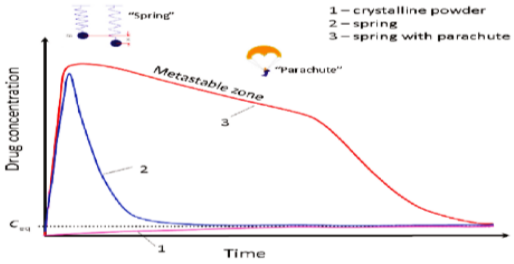

Figure (4): Spring and parachute model [30]

The spring and parachute effect can be described using a three step- mechanism proposed by Babu and Nangia, shown in Figure 5, this mechanism can be summarized by:

a. Cocrystals dissociate into amorphous or else nanocrystalline drug clusters, causing the immediate spike in drug concentration, which is known as spring effect.
b. Phase transformation into a metastable form, implementing Ostwald's Law of Stages.
c. Sustained increase in aqueous medium drug concentration, which is termed as per the 'parachute' effect [75].

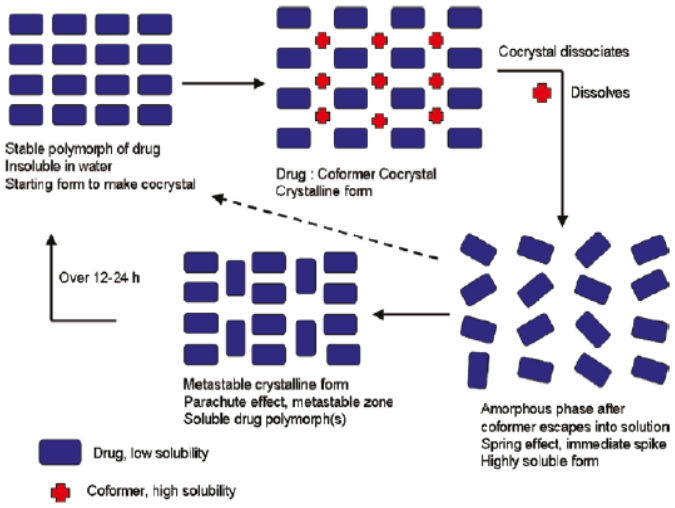

Figure (5): Proposed mechanism for dissolution of pharmaceutical cocrystals [76]

Dissolution rate lowering of cocrystals

Cocrystallization can also results in lowering the dissolution rate. This effect occurs primarily through modulating molecular arrangement in the crystal lattice into a denser and stable packing. This approach was adopted by several studies as sulfacetamide [77], fluoxetine HCl [78], curcumin [79], and lamotrigine [80] cocrystals.

Commercially available cocrystals

Pharmaceutical cocrystals have been investigated over the last two decades. However, only two pharmaceutical cocrystals have reached the market due to many hurdles for commercialization. One of which is the co-former selection since it is mainly relay on trial and error, which is both labor intensive and time overriding. Another obstacle is that there are no fixed scale-up procedures for the manufacture of pharmaceutical cocrystals as well as the setup of pharmaceutical cocrystal with high purity [44, 81].

Entresto™ (valsartan-sacubitril) by means of Novartis in addition to Suglat® (ipragliflozin-L-proline) via Astellas

pharma and Kotobuki pharmaceutical are the commercialized pharmaceutical cocrystals [82,83]

Entresto™ tablet is a multidrug cocrystal. It combines neprilysin inhibitor (monosodium sacubitril) with angiotensin receptor blocker (disodium valsartan) besides a water molecule. Entresto™ produced a higher bioavailability of valsartan than reference valsartan, and gained the Food and Drug Administration and European Medicines Agency approval in 2015 to treat chronic heart failure.

In Japan the Suglat® tablet has been accepted in 2014 on behalf of treatment of diabetes mellitus nevertheless has not obtained authorization in the United States or the EU. On the other hand, TAK-020 Cocrystal [83], tramadol-celecoxib [84] as well as ertugliflozin-L-pyroglutamic acid [85] are under clinical development.

Conclusion

Cocrystallization could be valued and encouraging method to modify physicochemical characteristics of APIs deprived of altering pharmacological activity. Simultaneous progresses in technology have permitted precise and fast structural characterization of innovative cocrystals. Consequently, in the near future it is worth to anticipate an increment in approved drug products containing pharmaceutical crystal.

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Conflicts of interest:

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Contribution of authors

Both authors contribute equally regarding conceiving and designing the study, collection the data, writing the manuscript. Both authors read and approved the manuscript for publication.

"We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors"

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