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Review Article

Multicomponent System: A Novel Approach in Cocrystal Techniques for Improving the Solubility of Poorly Soluble Drugs

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ABSTRACT

Poor solubility in modern pharmaceuticals has been a significant barrier to achieving optimal oral bioavailability. A majority of drug substances and New Chemical Entities (NCEs) are classified under BCS (Biopharmaceutical Classification System) Class II or Class IV. Cocrystals, which are multicomponent systems comprising an Active Pharmaceutical Ingredient (API) and one or more coformers in a specific stoichiometric ratio, have been utilized to address this issue. Furthermore, cocrystals and multicomponent systems have been developed to deliver Fixed-Dose Combinations (FDCs) of two or more drugs simultaneously, leading to the emergence of Drug-Drug Cocrystals (DDCs). They have helped in improving the bioavailability and efficacy of APIs by improving solubility and other factors such as tabletability and flow property. The eventual approval and the release of products such as Beta-Chlor, Suglat, Steglatro, Entresto, Setglujan, and Seglentis demonstrates the capability of DDCs to deliver fixed-dose combinations while achieving success in the market. This review provides a brief introduction to cocrystals as multicomponent systems and describes the feasibility of multicomponent systems, documented research on multicomponent systems and DDCs, identification methods and marketed approvals of DDCs.

Keywords: Cocrystals, Multicomponent Systems, Dissolution Enhancement, Improved Physicochemical Properties.

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INTRODUCTION

Despite the availability of numerous dosage forms in the market, oral solid dosage forms outnumber other products by more than 80%.[1] This can be attributed to factors such as ease of administration, improved patient compliance, and the availability of options, including immediate onset (buccal or sublingual tablets), conventional immediate-release, and delayed or controlled-release formulations, as well as the non-invasive nature of the route.

The dissolution, solubility and permeability of drugs play an important role in their absorption into the systemic circulation and their ability to elicit the required response.[2] Despite this, more than 90% of new chemical entities and 40% of marketed products belong to BCS class II (which shows poor solubility) or class IV (which shows poor solubility and permeability).[2] The solubility of an Active Pharmaceutical Ingredient (API) in an aqueous medium is an important characteristic as it helps determine the dissolution, permeability and bioavailability in the early stages of drug development. This step is essential in the initial stages of formulation development to design an appropriate formulation for use in preclinical and clinical phases of trials.

Due to the reduction in the discovery of new entities, pharmaceutical companies and formulators are developing newer modifications of existing drugs. The most commonly employed methods for enhancing solubility are techniques like salt formation, polymorphism, the pro-drug approach and the recently popularized cocrystal or crystal engineering approach.[3] The popularity of the cocrystal route comes from the advantage of producing combinations with higher solubility and improved stability which, in some cases, allows for an extension of the product's lifecycle.[3] However, the challenge remains to find the ideal combination of the API and coformer for the profitable production of a new and improved formulation.

The cocrystal approach can be understood as the modifications to the crystal lattice of solid API using non-ionic interactions. These

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non-stochiometric interactions can be non-covalent, namely π- π interactions, hydrogen bonding or Van der Waals forces. Cocrystals can also be better understood as a crystal composed of two or more components in a definite stoichiometric form. A typical cocrystal consists of one (or more) API and a coformer which is chosen from the list of non-toxic and inert components listed under the Generally Regarded as Safe (GRAS) list issued by the USFDA.[4] The cocrystal approach offers significant advantages, namely the access to a diverse range of coformers and the capacity to modify the physicochemical properties of the formulation without compromising the therapeutic efficacy or pharmacological profile of the API.

The first documented cocrystals were the accidental discovery of a cocrystal of urea and NaCl in 1783.[5] From there, the gradual but significant progress in the field of cocrystals, particularly in medicine, gained the attention of the USFDA. In 2011, they released the first draft of guidance that characterized pharmaceutical cocrystals drug product intermediates.[4] This led to the eventual approval of Odomzo®, Steglatro®, Suglat®, Entresto®, Beta-Chlor® and Seglentis® which was released on 14 Feb, 2022.[6]

Extensive research into the field of cocrystals has led to breakthrough discoveries like Drug-Drug Cocrystals (DDCs) an application of multicomponent systems, which consist of both components of a cocrystal being different APIs. This helped in the development of Fixed Dose Combination drugs (FDCs) which are capable of multiple targeting.

MULTICOMPONENT SYSTEMS: FEASIBILITY AND EVIDENCES

Multicomponent system is a term generally used to describe any system comprising of multiple constituent species. A defining characteristic of multicomponent systems is that the interactions between their constituent groups are non-covalent in nature. Depending on the specific type of interactions they can further be classified as salts or cocrystals. In salts, the system is composed of two or more species linked together by ionic interactions. These ionic interactions generally involve exchange of protons. Due to the smaller size of these protons, there is little to no stearic changes involved in the formation of salts. Crystals are comprised of multiple species linked together by weak H-bond interactions. These hydrogen bonds persist throughout the system and hence there are a lot of stearic changes involved during cocrystal formation. This section describes briefly the hydrogen bonding process and feasibility of these multicomponent crystals.[7,8]

The basic requirement for crystal formation is complementarity. It governs molecular association which can be expressed in several ways like lock and key mechanisms, hydrogen bonding donors and acceptor groups, ionic donor and acceptor groups, bumps and hollows and so on. Crystal nucleation and growth are also dependent on these factors. The basic principle of multicomponent crystallization is that the crystallization process is governed by a variety of physical, chemical and stoichiometric factors and through deliberate crystal engineering, it is possible to modify one or more of the above factors to synthesize crystals which consist of components which crystallize under different conditions when present in pure forms. After the development of XRD, it was established that the formation of multicomponent cocrystals is primarily influenced by the chemical and geometric configurations of the constituent components involved.[7,8]

This led to the discovery and understanding of DDCs which are capable of modifying the physicochemical and pharmaceutical properties of two or more APIs crystallized into a distinct crystal. DDCs can be defined as cocrystals where two or more components of the cocrystals are APIs. This allows the administration of multiple drugs in a single dose while subsequently improving the bioavailability and therapeutic efficacy. Despite growing interests in the field of DDCs one of the biggest drawbacks in DDCs is the lack of literature which severely reduces the chances of success as very little is known about the synthesis of successful DDCs.[9] DDCs opened up a new possibility in delivering fixed-dose combinations while reducing the strain in the formulation of different pharmaceutical combinations, which require a larger and more diverse number of excipients and also successfully improving solubility, dissolution bioavailability or the physical stability of drugs.

Extensive research into multi-component systems has resulted in a number of reported DDCs of NSAIDs, anti-tubercular drugs, anti-diabetic drugs, anti-neoplastic drugs, and anti-convulsant, anti-hypertensive and so on.

Co-formers and their selection based on multicomponent systems

The coformer is ideally selected from the list of "Substances added to food", formerly known as "Everything Added to Food in the United States" (EAFUS). This list contains all the food and colour additives aproved for use in the US, which roughly number over 3000, along with the "Generally Regarded as Safe" (GRAS) substances. The list for GRAS currently includes over 370 items and also dictates the safety margin for the use of the mentioned coformers and classifies them based on their safety into 5 categories/ types (Type 1, Type 2, Type 3, Type 4, Type 5).[10] The use of coformers not mentioned in the above list is allowed, provided that sufficient information on the safety and toxicity of the coformer (Both alone and in combination with API) has been thoroughly examined and made available for the regulatory authorities.

The screening for the coformers is of major importance as it determines the stability and functionality of the cocrystal being manufactured or researched. Previously popularized methods for coformer selection were focused on the trial-and-error approach

or knowledge-based approach.[10] Another method which was previously popularized was the use of "tactless" methods which compared a list of previously approved or accepted pharmaceutical cocrystals in order to obtain hints or clues for the formulation of newer combinations of API and conformer.[11] However, modern methods or newly popularized methods for screening of suitable coformers include hydrogen-bonding tendencies, pKa-based models, calculations of the crystal lattice energy of the resulting cocrystal, quantum chemistry-based thermodynamic methods like COSMO-RS (Conductor-like Screening Model for Real Solvents), measuring saturation temperature, Hansen solubility parameter, synthonic engineering, Kofler contact method which is used to monitor phase transitions and other complex thermal analysis. Another newer screening method which has gained popularity is the use of the Cambridge Structural Database.

The selection of the coformer and the method employed for its identification are at the discretion of the formulator. Approaches such as hydrogen-bonding tendencies, pKa-based models, Hansen solubility parameters, and synthonic engineering have demonstrated varying levels of success but come at the cost of a fair number of trial runs in formulating and characterizing the produced cocrystals. However, for commercial applications, computational models like COSMO-RS, COSMO-Therm, CSD, and Schrödinger provide high-throughput screening of multiple coformers against one or more APIs, thereby reducing costs by minimizing the number of trials required to identify a suitable coformer. These models can also offer detailed insights into various nonbonding interactions and the resulting stoichiometry, with a high degree of predictive accuracy.[7,8,10]

Theoretical Feasibility of multicomponent crystals

The theoretical basis for the formation of multicomponent crystals is the hierarchy followed by hydrogen bonding. When two molecules are interacting to form a hydrogen bond, a certain hierarchical pattern is followed which is decided as follows; the best hydrogen bond acceptor interacts with the best hydrogen bond donor and the second-best hydrogen bond accepting functional group interacts with the second-best hydrogen bond donor functional group and so on. However, the practicality of providing specificity to π- π interactions, ionic interactions and hydrogen bonding interactions proves to be the greatest challenge in creating multicomponent cocrystals. The only viable approach is to control the conditions in which these bonds are formed in order to selectively strengthen some bonds or selectively weaken others. This makes two-component cocrystals relatively easier to synthesize.

Three component systems

Three-component systems are somewhat more challenging to synthesize, as the interactions between the three constituents must be precisely controlled. Strong interaction between only two constituents will result in the crystallization of a binary crystal and if the interactions are too weak then each of the three constituents will crystallize separately. It has been observed that due to the characteristic of the kinetic factors involved in crystallization, hydrogen bonds between three component cocrystals form in a hierarchic mode. The simplest method for synthesizing a three component cocrystal is by incorporating an intermediate/bridge molecule having both hydrogen bond donor and acceptor sites. This bridge molecule forms complimentary hydrogen bonds with two different APIs. This method has been illustrated in Figure 1.

A method of synthesizing ternary cocrystals was explored by Song and team, who used $CaCl_2$ as an inorganic salt to crystallize levetiracetam/etiracetam with nicotinamide/isonicotinamide. The salt was used to form an inorganic salt bridge between the two APIs as they crystallize leading to a ternary ionic cocrystal.

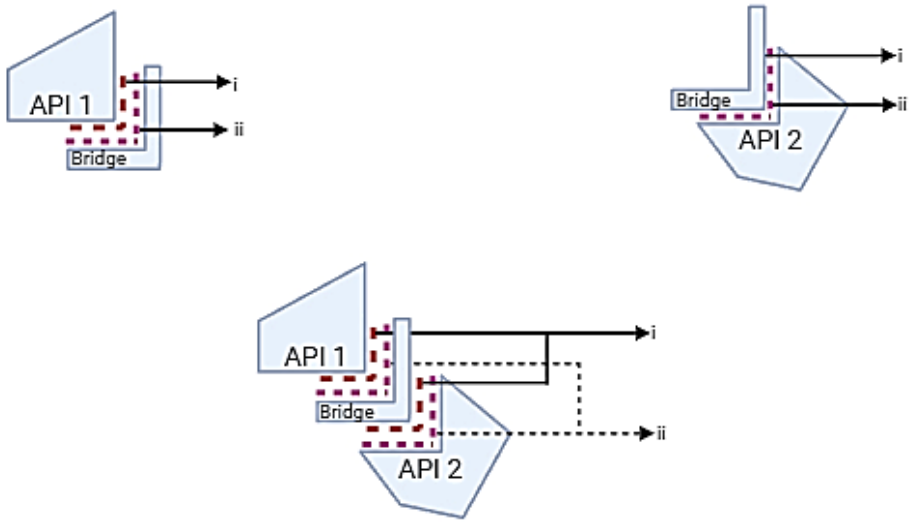

Figure 1: Pictorial Illustration of three component cocrystal. Within the Figure, i is the hydrogen bond donor sites and ii is the hydrogen bond acceptor site respectively.

The method involved synthesizing binary cocrystals between one group and $CaCl_2$ and then using the binary ICC to synthesize a ternary cocrystal using the remaining group. They synthesized three ternary cocrystals- levetiracetam -nicotinamide (2:1), levetiracetam -isonicotinamide (2:1) and etiracetam isonicotinamide (2:1). All of these were ternary cocrystals where the $CaCl_2$ acted as an inorganic bridging molecule and also incorporated a molecule of water. The study showed that the stereochemistry played an important role in cocrystal formation and hence there were no ternary ICCs formed between etiracetam and nicotinamide. It also showed that water was very crucial to the cocrystal formation and trace amounts of water was enough to stabilize the synthesized cocrystals. The Ca^{2+} atom within the cocrystal always assumed an octahedral configuration and the minor changes between the ternary cocrystals were attributed to the different functional groups or atoms which interacted with the octahedral calcium atom. As a result, all the cocrystals were synthesized at a ratio of 2:1:1 (levetiracetam: nicotinamide/isonicotinamide: $CaCl_2$ respectively). The ternary ICC was evaluated and it showed that cocrystallization impacted the stability of both the involved groups. It also showed that the dissolution of the ternary ICCs was reduced as compared to the binary counterparts, however the investigators recommended *in vivo* testing to study the effects this can have on bioavailability.[10]

Four component systems

Four component crystals are possible, but by nature require even more strenuous control over the crystallization conditions and reactants. There have only been up to 20 four-component crystals which have been reported to date, attesting to the complexity of the process involved.[12] A widely employed method for the discovery and synthesis of quaternary cocrystals is the strategy of structural inequivalence. This strategy states that when a constituent is situated in two different crystallographic environments within the same crystal structure, then it is possible to substitute it with a different constituent within the same crystal. This is further illustrated in Figure 2.

A quaternary cocrystal which showed unique properties was synthesized by Paul *et al.* They synthesized a quaternary cocrystal using resorcinol, tetramethylpyrazine, phenazine and pyrene. The author used a complex set of techniques including Long-Range Aufbau Module (LSAM), which is a concept utilizing small synthons for the deliberate designing and synthesis of larger stoichiometric cocrystals. During this synthesis, binary cocrystals of resorcinol and phenazine at a ratio of 1:1 was synthesized first followed by a ternary cocrystal of resorcinol, phenazine and pyrene which were synthesized using tetrahydrofuran. It was found that it was not possible to generate a quaternary cocrystal from a ternary cocrystal due to the structural modification induced by pyrene molecule. Finally, a quaternary cocrystal was grown by combining all the compounds together in 1:1 ratio of nitromethane: benzene as solvents. It was found that a yellow binary cocrystal of resorcinol: phenazine followed by epitaxtal growth of a reddish quaternary cocrystal which grew on the surface of the binary cocrystal. Through analysis of the quaternary cocrystal, a new and unusual arrangement of the MacGillivray synthon was observed. It has two different bases (tetramethylpyrazine and phenazine) as bridging pairs instead of the usual arrangement which had the same molecule as bridging pair. The investigators postulated that the formation of the quaternary crystal and the anomalous MacGillivray synthon was dependent on the binary cocrystal. It was also observed that the exposed crystal face of the binary crystal was significant in the synthesis of the quaternary crystal as the exposed surface served as a better fit for quaternary crystals than any ternary crystals which could be created.[13]

Five component systems

A five-component system is considered the theoretical maximum number of components which can be crystallized together because it would be practically impossible to find more than five molecules which can interact in a hierarchical fashion and the conditions and delicacy involved in synthesizing a cocrystal with more than five constituents would be very difficult to sustain and maintain.[7]

Documented research on multicomponent cocrystals and drug-drug cocrystals; recent works

The reports of DDCs have been increasing steadily since the past few decades due to the increasing popularity in the use of DDCs to deliver FDCs for specific or general disorders. The major works of DDCs have been elaborated, including DDCs of Non-Steroidal Anti-Inflammatory drugs, anti-tubercular drugs, diabetic drugs, anti-neoplastic drugs, anti-convulsant, anti-hypertensives and so

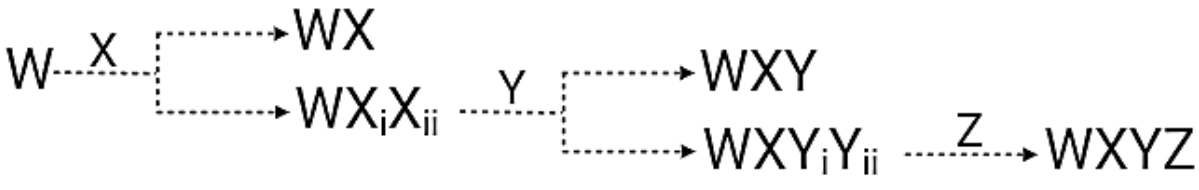

Figure 2: Pictorial Illustration of structural inequivalence as a method of discovery of higher cocrystals. Legend: WXYZ denote various chemical entities (API/Coformer) and i,ii denote various crystal environments.

on. A few of the recent works done on DDCs have been discussed below.

DDCs of dihydromyricetin and pentoxifylline

Liu *et al.*, reported a hydrated cocrystal of dihydromyricetin and pentoxifylline. The cocrystal was prepared by the slurry method and subjected to XRD. The analysis revealed that the cocrystals were formed during hydrogen bonding interactions between dihydromyricetin and pentoxifylline. Dissolution studies showed that the dissolution of pentoxifylline decreases greatly and that of dihydromyricetin increases slightly. This modification allowed for a sustained-release dosage form with a modified release pattern.[14]

DDCs of metformin and salicylic acid

Bhatt *et al.*, prepared cocrystals of metformin HCl and sodium salicylate using the solvent evaporation method and analyzed them using PXRD, thermal analysis and ATR-FTIR. After formation, the cocrystals showed improved tabletability as compared to pure metformin due to increased deformation and tabletability.[15]

DDC of furosemide and pentoxifylline

Stepanova *et al.*, prepared cocrystals of fenofibrate and pentoxifylline for use in cardiovascular indications. Pentoxifylline is used as a vasodialator and fenofibrate is used to treat pain caused due to low blood flow which can be caused due to obstructed arteries in the limbs. They produced three cocrystals, namely, a cocrystal, a cocrystal hydrate and cocrystal solvate using acetone all in a ratio of 1:1. The study revealed that the chemical environment was significant in impacting the cocrystal formed and the resulting structural confirmation. This can be seen in the hydrate form where the water molecules form a long chain along the crystallographic axis mainly involving bonds between O and H groups, whereas the acetone solvate consists of N and H as the significant bonds with acetone precipitated and bonded with amino group of fenofibrate.[15]

DDCs of azithromycin with paracetamol

Ul Islam *et al.*, synthesized cocrystals of azithromycin, an antibiotic, along with paracetamol, a selective COX-2 inhibitor. Solvent evaporation method was used to synthesize the cocrystals at a ratio of 1:1. The cocrystals showed thermal stability up to 240°C and also showed better dissolution. The cocrystals also showed better anti-microbial activity than the conventional azithromycin. This DDC shows particular applicability because generally anti-biotics are prescribed with anti-pyretic and anti-inflammatory drugs. However, the investigators said that the confirmation of the therapeutic activity *in vivo* is necessary to validate the *in vitro* results.[16]

Multicomponent cocrystals of sulfonamide with β-lactams and pyridine amides

Bolla *et al.*, synthesized a tertiary cocrystal containing sulfonamide along with β-lactams and pyridine amides using various methods. The methodology involved making an initial binary cocrystal and finally adding the third ingredient under highly controlled conditions. They investigated all relevant combinations in order to assess the reproducibility of the synthon and the stability of the tertiary cocrystal. The study revealed that a similarity in the size and shape of molecules involved in cocrystal formation helps in forming a reproducible synthon for crystallization. Another factor which impacted the formation of cocrystals is the solubility of the involved compounds where the authors observe that the third component must have lower solubility than the first two components alone and in cocrystal formation. Finally, the hydrogen bond between the first two components should show more bond specificity than that of the third component.[17]

PHYSICOCHEMICAL IDENTIFICATION AND CHARACTERIZATION

The physicochemical analysis of the cocrystals is an absolute necessity to ensure that the produced cocrystals are genuine. They should also display different physicochemical properties or pharmaceutical properties from a simple mixture of the API and coformer involved. They have also been reportedly used as tools to confirm the crystallization and observe the kinetics during the process of cocrystal synthesis.[3] The various methods used for analyzing cocrystals are mentioned below along with some examples.

Fourier Transform Infrared Spectroscopy

FTIR, short for Fourier Transform Infrared Spectroscopy, is the first routine analytical tool which is used to analyze cocrystals. FTIR is useful in determining the characteristics of the cocrystals and predicting the chemical composition of the cocrystals produced. It helps in differentiating the cocrystal from the salt or simple mixture of constituents by analyzing and characterizing the presence and extent of hydrogen bond formation between the API and coformer.

Gang-Chun Zhang and team performed a spectral curve fitting investigation on cocrystals of indomethacin and saccharine using thermal and FTIR analysis in order to analyze the formation and stability of the cocrystal formation process. The FTIR analysis revealed the formation of 5 new peaks between the spectral range of 3800-2500cm^{-1} and 3 new peaks between the spectral ranges of 1800-1600cm^{-1}. These peaks were seen in the time dependent spectral analysis performed simultaneously with co-grinding of the homogenous mixtures of indomethacin and saccharine. These new peaks can be attributed to the non-ionic hydrogen bonds which are formed during the cocrystallization process and

this can also be confirmed by their appearance after the 15-30 min of cogrinding.[13]

Differential Scanning Calorimetry

Another frequently used method of analysis of cocrystals is Differential Scanning Calorimetry (DSC). This process involves adding a measured amount of cocrystals and a physical mixture onto an aluminum pan and heated at a suitable temperature range. The resulting exothermic peaks of the cocrystals and physical mixtures are examined. The presence of a distinct exothermic peak, in contrast to the two separate peaks, can serve as a definitive indication of cocrystal formation. Other observable characteristics in DSC are glass transition temperature, melting point, the heat of fusion and polymorphic nature.

A novel application of DSC in cocrystal analysis involves identifying any incompatibilities between cocrystals and other excipients when used together in a formulation. This can be seen in the study conducted by Arabian *et al.*, who used DSC and PXRD to study the compatibility of various excipients with brexpiprazole-catechol cocrystal. DSC helped identify the compatibility between the cocrystal and PVP as there was a marginal reduction in the melting endotherm of the cocrystal.[18]

Thermo Gravimetric Analysis

Thermo Gravimetric Analysis (TGA) is another tool which can be used to analyze the compatibility, thermal stability and purity of cocrystals. It can also be used to understand the hydrates/solvates of cocrystals, presence of volatile compounds, decomposition temperature and sublimation temperature. The loss in weight during a TGA analysis can be a clear indicator of the decomposition of cocrystal or loss of one or more constituents.

The use of TGA in cocrystal analysis can be seen in a study conducted by Guo *et al.*, who used TGA among other techniques to analyze the synthesized cocrystals of nicorandil with 4 coformers. TGA analysis showed that the thermal decomposition of the pure form of nicorandil was lower than the produced cocrystals and this helped understand the higher thermal stability of the cocrystals as compared to pure drug when subjected to accelerated stability studies. The amount of unchanged drug in pure nicorandil after stability studies was found to be 2% in 20 days while the produced cocrystals were able to retain up to 92.2% of drug after 30 days.[18]

Solid State NMR

Solid State NMR is another technique which can be used to characterize the complexes by determining the degree of proton transfer within the constituents. SSNMR is used frequently for the identification of salts and cocrystals by identifying hydrogen bonds and local conformation changes.

A more advanced form of SS-NMR is the use of Cross-Polarization Magic Angle Spinning NMR in which the sample is placed at the "Magic" angle of 54.74° measured along the static magnetic field and spun. This can be seen in a study conducted by Shukla *et al.*, who used this SS-NMR, FTIR and Raman spectroscopy to perform structural investigations on nitrofurantoin and 4-hydroxybenzoic acid cocrystals. The C^{13} CP-MAS SS-NMR revealed few slight shifts when comparing the cocrystals with their individual components. This was attributed to the change in chemical environment immediately after the cocrystal formation. Each distinct carbon is signified in its individual peaks and similar carbons are represented by a single peak. Thorough analysis revealed that the cocrystal was not a physical mixture of the components. It also showed that there were no significant impurities present after synthesis.[19]

Powder X-ray Diffraction

Powder X-ray Diffraction (PXRD) is also a commonly used analytical technique for the analysis of powder samples of the cocrystals or other physical mixtures. The X-ray diffraction technique is used to elucidate the structure and crystal lattice arrangements of powder compounds. Cocrystals can be differentiated from their constituents based on a different pattern observed on the diffractometer as compared to the API and coformer. The most common type of PXRD used is the Single X-ray diffractometer.

A popular method of performing cocrystal analysis is by validating SSNMR results with PXRD to better ensure the absence of errors arising due to similar chemical shifts from different crystal packing arrangements. Sardo *et al.*, performed structural determination on a diazole-based powdered cocrystals which showed a distinct helical bonded network. They used PXRD in combination with SSNMR and DFT calculations to build and validate the structural model. In this study, the use of PXRD in combination with various SSNMR techniques helped distinguish the unusual bond distance between hydrophobic methyl groups.[20]

TeraHertz Time Domain Spectroscopy

An alternative to PXRD is TeraHertz Time Domain Spectroscopy (THz-TDS). THz-TDS is a spectroscopic analytical technique in which the molecules being analyzed are probed with radiation of TeraHertz frequency. This technique is also highly suitable to identify and distinguish a specific chiral configuration of a drug/molecule from a racemic mixture.[21]

A novel application of THz-TDS can be seen in a study conducted by WANG *et al.*, where they investigated cocrystals of pyrazinamide with 3-hydroxy benzoic acid. This investigation was carried out using THz-TDS and Raman spectroscopy. THz-TDS revealed that the cocrystals produced different peaks (in TeraHertz range) as compared to the physical mixture of pyrazinamide with 3-hydroxy benzoic acid. The investigators also highlighted a possibility of using THz-TDS for solid state crystal fingerprinting because the analysis showed near identical outputs

for the same cocrystal synthesized through two separate methods (solvent evaporation and neat grinding).[22]

A novel method which is receiving recognition in the analysis of cocrystals is Systemic Computational Analysis (SCA). In computational analysis, data from other spectrometric methods, namely THz-TDS, is entered into a software program which uses the specified spectrometric data to analyze and draw conclusions over the energetic parameters, London dispersion forces and provides a detailed description of the hydrogen bonding scheme of the cocrystals.[10]

MARKET APPROVALS

The popularity of multicomponent cocrystals has grown over the recent years due to the success of various DDCs in the market. Some examples of market approved DDCs and multicomponent systems are;

Chloral-Betaine® (beta-chlor) is a combination of chloral which is used as a sedative and betaine is an endogenous substance which modifies metabolism. This cocrystal was discovered accidentally in 1962 while trying to mask the bitter taste of chloral but was only recognized as a cocrystal in 2016. Beta-chlor cocrystals can be synthesized in two polymorphic forms. The α form of the cocrystal appears as prismatic cocrystals produced by simple solvent evaporation whereas the β form can be obtained by repeated melting of the α form of the cocrystal to 60°C and cooling to room temperature repeatedly to give larger, more stable needle shaped crystals.[23]

Suglat® (Ipragliflozin L-proline) is a cocrystal produced by Astellas and Kotobuki pharmaceuticals and is the first Sodium-Glucose Cotransporter 2 (SGLT-2) inhibitor which was approved in Japan. The major factor responsible for its formulation as a cocrystal was the hygroscopic nature of ipragliflozin and its ability to switch from amorphous to non-stoichiometric hydrate form depending on storage conditions. The improved stability by cocrystallization contributed to the widespread success of Suglat®.[24]

Entresto® (valsartan-sacubitril) was one of the first approved DDC launched by Novartis. Although Entresto® is a more costly option compared to other available treatments, the enhancement of bioavailability and improved pharmacokinetics have contributed to the market success of this product since its introduction.[25] Entresto is a salt cocrystal consisting of valsartan, an angiotensin receptor inhibitor and sacubitril, a neprilysin inhibitor and is also a hydrate, containing water molecules which stabilize the cocrystals. It is a salt-cocrystal supermolecular complex and it can be synthesized in 6 forms under different solvent systems or crystallization environments. Of these, forms 1-3 showed lower hygroscopicity and better stability.[26]

Steglatro® is another combination containing ertugliflozin, another SGLT-2 inhibitor which has been crystallized using L-pyroglutamic acid. This cocrystal was produced by high throughput process and computational screening to solve the problems regarding the crystallization of ertugliflozin. It was developed by Pfizer and Merck in collaboration and was approved in 2017.[27]

Steglujan® (ertugliflozin and sitagliptin) is another example containing ertugliflozin (9SGLT-2 inhibitor) and sitagliptin (a dipeptidyl peptidase inhibitor) for the treatment of diabetes mellitus. The success of this multi-drug combination in the market also demonstrated the effectiveness of cocrystals in achieving market success.[28]

Seglentis® (tramadol celecoxib) is the newest approved cocrystal in the market which was released on February 14th, 2022. This is a multi-drug combination contains tramadol, an opioid analgesic combined with celecoxib, a selective COX-2 inhibitor. It was prescribed to treat moderate to severe acute pain.[29] Like Entresto, Seglentis is also an ionic salt cocrystal consisting of an ionic chlorine bridging tramadol and celecoxib in the synthon. The chlorine is involved in ionic as well as hydrogen bonds and is essential to stabilize the cocrystal structure.[30]

CONCLUSION

Multicomponent systems and cocrystals have proved to be a versatile approach in improving the solubility, stability and physicochemical properties of various APIs. They have also proved to be effective in delivering FDCs and the success of various multicomponent cocrystal products like Setlujan®, Entresto® and the most recent Seglentis® also attributes to the development of research to discover similar DDC combinations.

The biggest hurdle in development of multicomponent systems and DDCs is the lack of deliberate research to predict the formation as well as a lack of knowledge in the means of synthesis. The impact of various manufacturing techniques and scale-up procedures on the effectiveness of DDC combinations also proves to be a significant barrier in the development of cocrystals and multicomponent systems.

Despite these setbacks, cocrystals and multicomponent systems continue to be an emerging field in the development of stabilized therapies and more advanced formulations. The discovery of green techniques and mechanochemistry has been recently used in the production of multicomponent systems. Further research into cocrystals and multicomponent systems can lead to the development of cost-friendly, effective and safe therapies for various disorders like cancer, retroviral disorders, lifestyle disorders like hypertension and diabetes and can also led to improved patient compliance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GRAS: Generally Regarded As Safe; **EAFUS:** Everything Added to Food in the United States; **DDC:** Drug-Drug Cocrystals; **FDC:** Fixed Dose Combination; **COSMO-RS:** Conductor-like Screening Model for Real Solvents; **CSD:** Cambridge Structural Database; **SCFL:** Super Critical Fluid; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** Differential Scanning Calorimetry; **TGA:** Thermo Gravimetric Analysis; **NMR:** Nuclear Magnetic Resonance; **PXRD:** Powder X-ray Diffraction; **THz-TDS:** TeraHertz Time Domain Spectroscopy; **SCA:** Systemic Computational Analysis.

SUMMARY

Multicomponent systems, a novel approach in cocrystals, offer an advanced approach for the improvement of the solubility and bioavailability of BCS Class II drugs. It also provides the scope for formulators to further improve or modify various physicochemical properties depending on the choice of various coformers. Also, the manufacturing process or changes in the specific conditions associated with the formation of cocrystal in multicomponent systems impact the final product significantly. The ability to incorporate multiple APIs into a single cocrystal may be useful in FDCs (Fixed Dose Combinations) for the treatment of complex disorders like tuberculosis, diabetes, hypertension and various cancers. This review covers a brief introduction into multicomponent systems in cocrystals which includes the theoretical feasibility, various forms of multicomponent systems and evidences supporting the same. It also covers some DDCs (Drug-Drug Cocrystal) seen in recent literature along with characterization techniques and market approvals for multicomponent cocrystals as pharmaceutical products.

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