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REVIEW ARTICLE **OPEN ACCESS**

A Rational Review of the Recent Developments and Assessment Methods in the Field of Co-Crystals

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ABSTRACT

Pharmaceutical co-crystals consist of multiple elements like two or further molecules which are held by a Hydrogen (H) - bonding. At present, co-crystals give an amazing chance for advancement and manufacturing the new formulations by improvement in their physical properties. In the course of making new products, there is a lack of solubility in water and negligible oral ability to be absorbed by the body. Considering new studies, co-crystals are classified as a poly-morph drug, but as an indifferent API which has influence on developing drugs. The process used to diminish its low aqueous solubility is crystallization which improves the various properties like melting point, its tabletability, bio-availability, solubility and its stability, whilst not harming the active pharmacological aspect of the pharmaceutically manufactured drug. Numerous techniques are devised for preparing co-crystals namely, grinding, slurry, anti-solvent, sono-crystallization, supercritical fluid process, hot melt extrusion and freeze drying. This article discusses all of these in depth. It also focuses on the other techniques in the synthesis and formulation of better co-crystals. We also assess the co-crystals through standard analysis like the spectroscopic analysis, terahertz spectroscopy, solid state nuclear magnetic resonance, thermal gravimetric method amongst the many. The variously used techniques are mentioned along with their pros and cons through the features like crystal quality, its purity and its stability, throughout and the hurdles in large scale manufacturing.

Keywords: *Pharmaceutical co-crystal, Co-crystallization, solubility, Bioavailability, solvent evaporation, Freeze drying, Terahertz Time-Domain Spectroscopy, Hansen Solubility Study*

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INTRODUCTION

Due to the underlying fact that a vast number of medicines are manufactured and retailed in solid forms, improvement in their physical properties is of great curiosity to pharmaceuticals. The physical appearance properties of a pharmaceutical drug in consideration affect factors like processing, delivery and thus, the entire effectiveness of the medicine. Multi-component systems consist of not lower than one active pharmaceutical component and other pharmaceutically approved medicines, similar as in the pharmaceutically attained co-crystals formulations. The most emerging and encouraging proposal to better the effect of a drug, such as their solubility, dissolution profile, stability and, pharmacokinetics are the high aspects of co-crystallization of the drug substance and drug products [1-3].Co-crystals, which are physically solid that are neutral crystalline single liquid phase materials made up of two or further different molecules, are generally in an exceedingly stoichiometric proportion which are not solvates or simple salts [4]. If at least one of the co-formers is an API and also another is acceptable pharmaceutically, then it is said to be a pharmaceutical co-crystal [5]. co-crystals of various stoichiometries with the identical conformer are possible, as illustrated by the carbamazepine: 4-aminobenzoic acid co-crystal system, which might exist in 1:1, 2:1, and 4:1 stoichiometric configuration [6].A co-crystals encompasses a varied crystal structure, in comparison of the starting materials and as a results different physicochemical property. The

attractiveness of co-crystals is an underlying feature of its design, of a superior physical property because of its pure parent molecules. The improvement in the co-crystals via co-crystal formation has been demonstrated for solid explosives [7], agro-chemicals [8], pigments [9], and, particularly, pharmaceuticals [10 -15].

From recently discovered large numbers of drugs around 60-70% are related to the BCS Class II (High permeability and Low solubility) and IV (Low solubility and Low permeability) and cause difficulty related to dissolution, solubility, Stability, therapeutic efficacy etc. Today's need is to minimize the problems of its solubility and permeability of pharmaceutical drugs that have been available in different forms. Multi-component Crystals like solvates, hydrates, co-crystals, salts contribute to the main role in designing the new solids mainly in the Pharmaceutical sector [16-18].

PHYSICOCHEMICAL PROPERTIES CAN ALTER WITH CO-CRYSTAL TECHNIQUES

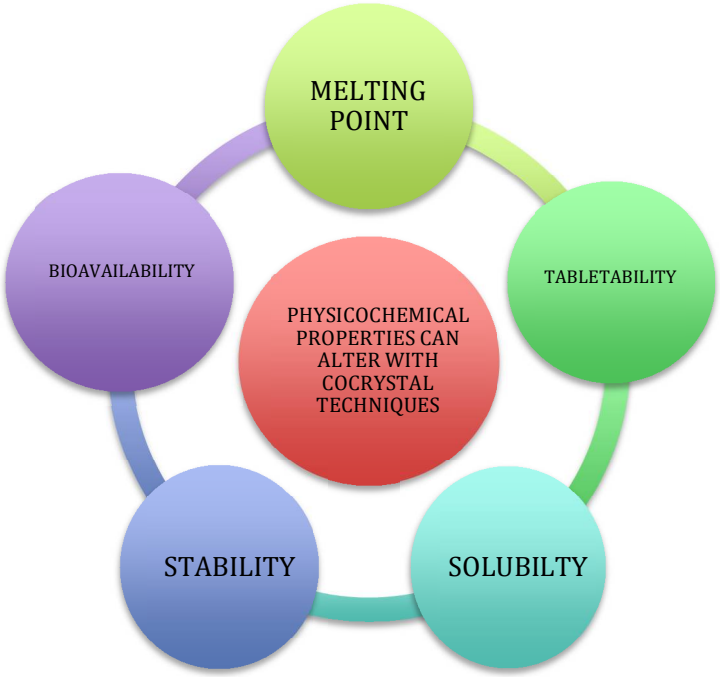

Fig. (1). Physicochemical properties that effect on co-crystal techniques

Melting point

The test for determination of purity and a physical property is co-crystallization. Its melting point lies within a narrow range of 18 selection of conformers is very crucial while considering the study of co-crystals as it provides better stability and is inculcated in thermo labile drugs. Hence, thermodynamic stability is important while selection of a drug and it can be verified through its melting point [19]. The most commonly known techniques for determining the point at which it melts are thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC). Zheng et al observed the synthesis under the co-formers Nicotinamide and saccharin, of the carbamazepine co-crystals. Two different separate solvents namely, water-ethanol solvent mixture and polyvinyl pyrrolidone (PVP) solution. The observer also reviewed the co-crystal's melting point under the influence of various scanning calorimetry and noted that in the DSC curve of the parent material which here is nicotinamide and carbamazepine as the solvent, ethanol water mixture; revealed its melting point near about 195°C and 132°C individually.

The co-crystals generated depicted a single endothermal peak near 162°C, which lies within the melting points of carbamazepine and nicotinamide. Saccharin and carbamazepine in ethanol-water solvent revealed their melting point as 176°C and 181°C, whereas the same of the generated co-crystals was 173°C [20]. Jadhav et al too analyzed the melting point of fenofibrate co-crystals made by different co-formers namely para-amino benzoic acid, benzoic acid, and salicylic acid. They further observed that the melting point of pure fenofibrate was around 78-82°C while the same for co-formers like para-amino benzoic acid, salicylic acid and benzoic acid was showcased around 184-186°C, 158-160°C and 122-124°C individually [21] Thus, the conclusion was that fenofibrate had a decrease in melting point, when compared with the pure one and the co-formers separately. Also, the co-crystals of piroxicam made with the help of sodium

acetate, saccharin sodium urea, nicotinamide, and resorcinol as co-formers were also noted by the virtue of difference in melting point of the pharmaceutical drug and its co-crystals. After co-crystals of piroxicam formed, its melting point was less when compared with sodium acetate, saccharin sodium co-formers, which were high individually. However, the melting point of co-crystals of urea, nicotinamide, and resorcinol saw an increment [22].

Tabletability

The capability to convert a substance into tablet form is named tabletability. One of the crucial criterion of preformulation study is crystal packing, tabletability and compaction. These properties are tested by the process of co-crystallization through suitable co-formers. Crystals of resveratrol were studied by Zheng et al under the co-former's 4-aminobenzamide and isoniazid. The outcomes helped to study its magnified solubility and tabletability [23]. It was noted by the researcher that tabletability of RES is not very impressive as at a high pressure of 0.6 MPa and tablet lamination, whereas the tablets prepared by co-crystals of Resveratrol-4-aminobenzamide, shows the tensile strength of 3 MPa at 250 MPa compaction pressure. Another researcher advised that development of the pharmaceutical co-crystals improves the tabletability feature of the drug. This behavior of paracetamol with trimethylglycine and the oxalic acid co-crystals were comparatively better, when compared with the pure drug. The performance of resveratrol can be improvised by the help of 4-aminobenzamide and isoniazid. The co-crystals provided a better level of tabletability when compared with the pure drug and the co-formers. By making variation in the mechano-chemical properties of APIs can be changed through co-crystallization of vanillin isomers with the same conformer presented a higher tabletability [24].

Solubility

As mentioned, while introducing the topic, around 60 to 70 percent of drugs come from the BCS Class II (High permeability and Low solubility) and the BCS Class IV (Low permeability and Low solubility) as well in previous study. Hence, it requires a betterment in solubility so as to work on various formulations. With improved co-crystals scientists can increase solubility of low soluble drugs and many scientists have already used this technique to improve the solubility of drugs. E.g., Given, Mounika et al, made co-crystals of fexofenadine through tartaric acid as the conformer, using the method of solvent evaporation and observed the benefits of saturation solubility by the Higuchi and Connors method. The researcher also worked on drug solubility studies including water and HCl in concentration of 0.01N and observed the reading of solubility of the co-crystals in water increased by 11 folds. Solubility of the pharmaceutical co-crystals in concentration of 0.01 N HCl is 2.47 times more than the parent drug [25]. Itan et al made Simvastatin-nicotinamide crystals by the solvent evaporation method to enhance its solubility of Simvastatin through co-crystallization of nicotinamide. The outcome contained a saturation in solubility of co-crystals showcasing an increment by 3 folds when compared with the parent drug. Also, Chadha et al too enhanced the soluble ability of efavirenz by the co-crystallization method [26].

Stability

Stability too, is an imperative study, which is necessary to be performed while developing a new medicine formula. Various studies like chemical stability, thermal stability, solution stability, photo-stability etc., are done in the developing stage of the co-crystals. Iyan et al made Simvastain-nicotinamide co-crystals by the method of solvent evaporation, with nicotinamide as an agent and noted that at 40°C and humidity 75% for one month made it stable [26].

Bioavailability

This is called the rate and extent of the drug which reaches into systemic circulation. APIs have a low oral bioavailability, which is a difficult task to develop formulations, which is done by the help of co-crystallization. Many scientists have made an improvement in the bioavailability of various drugs by converting them into co-crystals [27]. Example given, Mounika et al made co-crystals of fexofenadine that is from a class II (High permeability and Low solubility) drug, as given in the BCS classification. Hence, the researcher performed an experiment and made co-crystals of fexofenadine with a conformer namely, tartaric acid by the method of solvent evaporation. It was noted that through co-crystallization process, the drug had more released when comparedwith the formulation. Pinky et al also prepared co-crystals of clarithromycin in tablet form for increasing its bioavailability. Clarithromycin is a BCS Class II (High permeability and Low solubility) drug which was made by urea as a conformer using the method of solvent evaporation. Thus, the conclusion drawn was that the clarithromycin co-crystallized tablets had a better solubility and in vitro drug release profile in comparison to other marketed tablets. It also caused increased Oral bioavailability and therapeutic effect. Zhang et al too examined the synthesis of co-crystals of carbamazepine by the help of nicotinamide and saccharin through the method of solvent evaporation [28].

METHOD OF PREPARATION & REPORTED METHOD FOR COCRYSTAL PREPARATION

The process of making a co-crystal as mentioned in literature signifies the difficult situations where the system works for making the co-crystals. It generally takes around six months for preparing a single co-crystal which consists of the required quality for x-ray diffraction analysis. This can also be caused by the heteromeric system that consists of, which forms non-covalent forces between two or further molecules that are stronger than other molecules, in other corresponding homomeric crystals. The strategy for designing the specific co-crystal is still being studied, and the conclusion so far remains that it cannot be understood. Co-crystals can be formulated by the solvent and solid based method. The first method uses a slurry conversion, solvent evaporation, and cooling crystallization and precipitation. The second method uses net grinding, solvent- assisted grinding and sonication at 80 to 85°C.

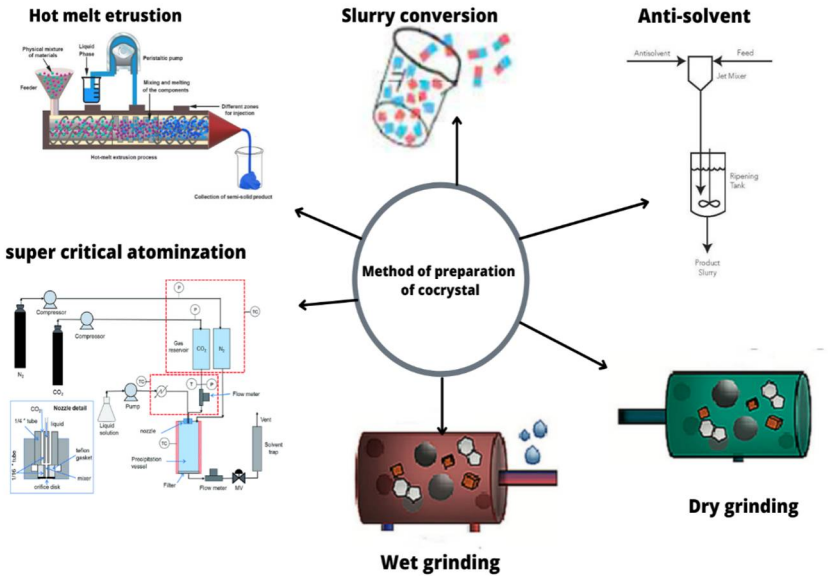

Fig. (2). Schematic diagram of method of preparation of co-crystal

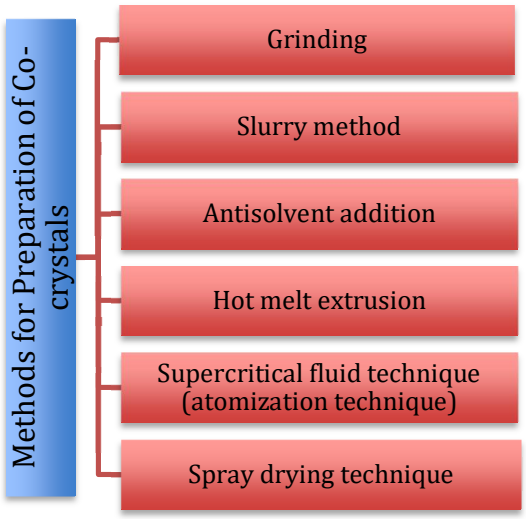

Fig. (3). Method of Preparations of co-crystal

Grinding:

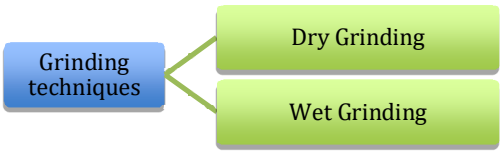

Fig. (4). Type of grinding techniques

Dry grinding & wet grinding

a) Dry grinding method

Step 1: Add both, the Pharmaceutical Drug as well as the co-former together (*In a specific stoichiometric ratio*)

Step 2: Grind (Using Mortar and the pestle or ball mill)

b) Wet grinding method

Step 1: Add the Pharmaceutical Drug and the co-formers together (In a specific stoichiometric ratio) *(Addition of drops of solvent in mixture)*

Step 2: Grind (Mortar and pestle or ball mill)

Sungyup et al synthesized Adefovirdipivoxil co-crystals under the influence of suberic acid and glutaric acid as conformers using a liquid grinding in assistance [29]. Prabhakar et al also prepared piroxicam co-crystals with sodium acetate as the co-formers, using the grinding method. They noticed changed properties of the cocrystals prepared from piroxicam and made orodispersible tablets, which have a better disintegration and the rate of dissolution [30]. Muhammad and others formulated ibuprofen amino acid co-crystals through the grinding and the (assisted) liquid grinding method. Gaikwad and fellow scientists prepared co-crystals of fenofibrate by the grinding method [31].

Slurry conversion method

The process of Slurry conversion

Step 1: Add the Drug as well as the co-former together *(In a prespecified stoichiometric ratio)*

Step 2: Addition of solvent to form slurry

This method, known as slurry conversion, was used across various organic solvents and water. A solvent of 100 - 200 ml quantity was added into a 20 mg co-crystal, and the solution was stirred for some days at room temperature. After an interval of certain days, the solvent gets decanted, and the remaining solid part was dried under nitrogen's influence for five minutes. The solid was then studied further using PXRD. DWI and other scientists prepared nicotinamide co-crystals through the method of slurry conversion. They added together, both powders of Artesunate and nicotinamide in a mortar and then added water to form a slurry [32].

Hot melt extrusion

Step 1: Add the Drug as well as the co-former together *(intense mixing)*

Step 2: Improves surfaces contacts without use of solvent

Step 3: co-crystal formed

(Not suitable for thermolabile drugs)

Hot melt extrusion drugs and co-formers are heated while they are intensely mixed without any solvent. Similarly, Li et al, analyzed the suspensions of ibuprofen/isonicotinamide cocrystal in a single-step hot-melt extrusion process [33]. Kevin and other scientists studied formulation of co-crystals of Carbamazepine through the Hot-Melt Extrusion. The author took help of Carbamazepine as the primary drug and nicotinamide in the role of a conformer and further studied the co-crystal matrix by the use of differential scanning calorimetry, powder X-ray diffraction, Fourier transform infrared spectroscopy [34].

Anti-solvent method

It is also a process for precipitation or recrystallization of the co-crystals formed and the active pharmaceutically determined ingredient. The solvents used are buffers (pH) and organic solvents. For preparation of aceclofenac co-crystals along with chitosan, where chitosan solution is made by soaking it in glacial acetic acid. Through a homogenizer, which has high dispersion, a calculated amount of drug is added in the solution containing chitosan. It is then mixed with distilled water or to a solution of sodium citrate for precipitating chitosan on the drug. Scientists like Momoko and certain others created co-crystals by anti-solvent addition method through the use of two sequences [39].

a) First sequence

Step 1: Carbamazepin rich poly-saturated solution feeded in crystallizer

Step2: Saccharin rich poly-saturated solution

(*Water was added into the solution*)

Step 3: Particles were sampled after addition of both the solvents

b) Second sequence

Step 1: Carbamazepin rich poly-saturated solution feeded in crystallizer

(*Water was added into the solution*)

Step 2: Saccharin rich poly-saturated solution
Step 3: Particles were sampled after addition of both the solvents

Supercritical fluid atomization technique

Step 1: Add Drug and co-former together
Step 2: Dissolve together in high pressurized supercritical fluid (CO2)
Step 3: Automize the solution with atomizer at normal temperature and pressure causes conversion of CO2 from liquid state to gas state
Step 4: Formation of co-crystals

Abhijat et al prepared and characterized Carbamazepine and Nicotinamide cocrystals by supercritical fluid process (SCF) [35] method and characterized developed co-crystals by the use of differential scanning calorimetry, also through dissolution studies, by hot stage microscopy and by the help of scanning electron microscopy, H NMR and X-ray powder diffraction [36]. Courtney and others performed analysis of synthesis of co-crystals of itraconazole as well as the succinic acid by gas anti-solvent (GAS) co-crystallization using pressurization. The author dissolved itraconazole along with succinic acid and mixed it in a liquid solvent (tetrahydrofuran) at favourable conditions and a pressurized solution of CO2, which decreases tetrahydrofuran's solvating power, and caused formation of crystallization of itraconazole–succinic acid co-crystals. Characterized co-crystals with the help of Fourier Transform Infrared spectroscopy, Powder X-ray diffraction, scanning electron microscopy and differential scanning calorimetry [37].

Ning and companions synthesized co-crystals of 2,4,6,8,10,12 hexanitrohexaazaisowurtzitane (CL-20) and 2,4-dinitro-2,4-diaza pentane (DNDAP) in a proportion or specific molar ratio of 2 : 1 through rapid and continuous spray drying method [38]. Amjad and others undertook preparation of Theophylline cocrystals by the technique of Spray Drying. Author also made the co-crystals of Theophylline in companionship of urea as well as saccharin and nicotinamide as primary ingredients through the spray drying technique with the help of numerous solvents containing varied solution concentrations where dying was done through nitrogen gas.

Table. (1). Advised method for preparing co-crystal

Drugs	Co-formers	Methods used for Preparing	References
Piroxicam	● Adipic Acid ● Benzoic Acid ● Cinnamic Acid ● Citric Acid, ● Glutaric Acid ● P-Hydroxybenzoic Acid ● Hippuric Acid ● Malonic acid ● Resorcinol ● Saccharine Sodium ● 1-Hydroxy-2-Napthoic Acid ● Sodium Acetate ● Urea ● Catechol ● Ferulic Acid ● Aerosil-200 ● Nicotinamide ● Para Amino Benzoic Acid ● Anthranilic Acid and ● Succinic Acid	Dry grinding method	[40]
Darunavir	● Succinic acid	Cooling crystallization	[41]
Aceclofenac	● Sodium Saccharin	Solvent-drop grinding method	[42]
Efavirenz	● Lactic acid and ● Adipic acid	Solvent evaporation	[43]
Felodipine	● Xylitol	Wet co-grinding	[44]
danazol	● vanillin	Solution crystallization	[45]
Clarithromycin	● Urea	Solvent evaporation	[46]
Myricetin	● Proline	Solution crystallization on The basis of ternary phase diagram principle	[47]

MECHANISM OF FORMANATION OF CO-CRYSTALS

It is advised that synthesis of fresh co-crystals is affected by various variables, and majorly by the properties of solvent and the reactants. Example given, existence of any functional groups and soluble ability of the reactants in any solvent along with many other experimental circumstances like its prespecified stoichiometric ratio of the co-formers and API, the temperature of the solution considered, the frequency of stirring, its pH and the type of glassware are the few effective parameters which are listed [49].

Whereas, the guidelines of hydrogen bonding, synthons and the graph sets can also be analyzed while developing the co-crystals system. For example, an API that has carboxylic acid in it, the co-formers to use should include moieties or amides, as they have higher chances of co-crystallization [50]. But it is not necessary in every case and provides absolutely no guarantee of a co-crystal formation. Hence, the formation of co-crystals is a multistage, which takes place in multiple stages and consists of an empiric procedure. As mentioned before, there are various ways in which co-crystal can be synthesized. But due to the lack of control over the nucleation process, crystallization, and the various phases in evolution of the co-crystal is a great scientific challenge [51]. The mechanochemical techniques are great techniques for production of co-crystallization from green chemistry and affordable synthetic pathways [52]. In the year 1893 grinding, for the very first time imbibed as the crucial way for co-crystallization and for producing Quinhydrone co-crystals through equimolar amounts of p-benzoquinone and hydroquinone [53]. After this various crystalline compound were formed through this mechanism of neat as well as wet grinding.

Even after all these technological advancements, the mechanism behind co-crystallization through this method has not, yet, been studied completely. Hence, numerous efforts were taken to understand the mechanism behind all these methods. Fox had suggested that formation at high temperature of about 1000 C for a short span of time [54]. Balaz had suggested the magma plasma model which provides the preparation of transient plasma could take place at 10000 C [55]. Negligible explanation is given for the stable nature of the conformer and the API at such high temperatures. Co-crystallization isn't a one-step mechanism process, as Jones and friscic had proposed [56].

According to them it consists of different mechanisms which includes molecular diffusion, eutectic formation [57] and co-crystallization via amorphous phase. The only common thing between all the pre-discussed mechanisms is the presence of an intermediate bulk phase [58]. For such mechanisms, there exists various examples in literature. It is also specified that molecular diffusion is more possible where one or both the reactants have a higher vapor pressure in solid state. Fresh surfaces also increase the molecular diffusion on the crystal. It should also be kept in mind that the mechanical force can hamper the intermolecular bonds present in the crystals of the reactant molecules. In other nominal cases, the solid and vapor/gaseous diffusion are almost same, for example, in co-crystals made up of naphthalene. But, while considering heavier aromatic hydrocarbons, surface diffusion is rather more effective for the entire co-crystallization procedure [59-65].

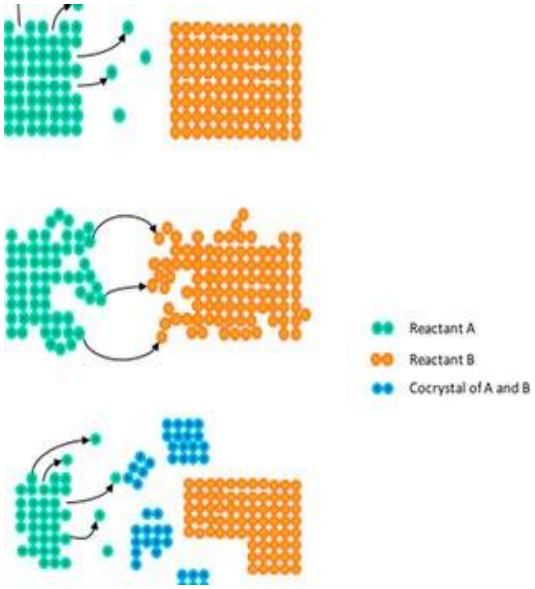

Fig. (5). Mechanochemical mechanism for crystallization of co-crystals [75]

ASSESSMENT OF CO-CRYSTALS [48]

Spectroscopic Analysis

Fourier-Transform Infrared Spectroscopy

This presents as the universally used procedure to predict and determine the chemical conformation, the interactions taking place intermolecularly and a mass study of the API and the conformer. The examination of API, the co-formers as well as the co-crystals are performed by FTIR, where the wavelength ranges between (400-4000cm^{-1}). This particular methodology is significantly quick, nondestructive, and is prone to further modifications in the molecular structure and can also help in detecting any functional group.

5.1.2. Terahertz Time-Domain Spectroscopy

This technique is similar to the diffraction of X-ray (PXRD) for distinguishing and identifying the co-crystals. It plays a helpful role in distinguishing the supra-molecular structures, chiral, and the racemic molecules that have a presence in the given co-crystal sample. The examples include different co-formers of theophylline's co-crystals.

Solid-State Nuclear Magnetic Resonance

NMR in the physically solid state is mainly used for its characterizing and identifying the various physically solid forms of pharmaceutical products and the associated co-crystals. this procedure recognizes salts, co-crystals and can also help in studying the structure by determining the change in local conformation, and the hydrogen bonds by coupling the basic principle that are utilized in this procedure is the nuclei shift by the irradiation, which differentiates the co-crystals from its excipients, with the virtue of this qualitative and quantitative method, we can understand the molar ratio of the mixtures in the reaction considered and the sort of hydrogen atom present in the given molecule.

Thermal Gravimetry Method

This particular technique is utilized for determining the sample weight under influence of temperature, under a specific interval of time. Differential scanning calorimetry: it is utilized in determining the co-crystal formation, which is determined by the presence of an exothermic crest followed by endothermic crest in the DSC spectra. The manufacturing of co-crystal is also determined through the presence of crests or peaks being found in the compound. It also looks helpful in determining its point of melting, its polymorphic nature, temperature of the glass, the heat of fusion involved in the reaction and endothermic or exothermic property of a compound and molecule. The analysis through the thermo gravimetric technique provides approximate drying temperature and all the numerous reaction steps involved in the presented component. This procedure is also used in considering the hydrated or solvated form of the crystals, detecting volatile compounds and in analysis of decomposition and/or sublimation caused by the co-crystals. The prediction of the purity, solvates/hydrates forms of the prepared co-crystals, their thermal stability and its compatibility are possible only through Thermal gravimetry method.

Hansen Solubility Study

This method, named as Hansen solubility parameter, is a major tool used in prediction of the miscibility property of a drug and co-former while forming the crystal, or of the excipients/carriers. It also helps in prediction of compatibility of the pharmaceutically considered materials involved, while the analysis is also considered in the pre-formulation and in tablet formulation. The energy of cohesion is used in predicting physicochemical properties like the point of melting and the solubility level of the compound co-crystals that are bonded together through a weak or non-existent hydrogen bonding which mainly are miscible at molecular level. In the solubility study, the varied types of solvents like water, buffer solution of different pH values, restoring intestinal fluid, and gastric fluid. It is a major parameter of drug testing for drug development.

Dissolution study

It is mainly defined as 'the amount of drug substance which changes into a solution in a recorded unit time under prespecified conditions of liquid-solid interface, composition of the solvent, and temperature.' In-vitro dissolution studies of a solid drug is done to study the efficacy of dissolution of a freshly formulated drug. It is carried out on the apparatus used for dissolution, in the available dissolution medium asper the official compendia. The samples taken at prespecified time periods are studied under the influence of HPLC or Ultraviolet spectrophotometer. The solubility study by the Higuchi and Connors method is performed in determining solubility of co-crystal. The solubility of the pharmaceutically synthesized co-crystals, that of the pure API and the physical mixture of API and the selection of conformer is diluted with water and various mediums as informed in the official compendium.

Stability Study

This examination, i.e. stability study, is one of the most important parameters in the scrutiny of co-crystals, as it provides information about the various conditions, climatically that it is stored in, the expiry date of the drug, or that of the ingredients used in the drug. There are different parameters that also can ruin the

stability of the drug namely, humidity level, exposure to light and surrounding temperature. Studies of stability are done at a distinct temperature, at various humid conditions for a predetermined time interval, which provides us with a clear description about the shelf life of a contemporary co-crystal.

CHALLENGES & OPPORTUNITIES

According to recent standards, the current market value of developing a drug is US$2.8 billion [66]. Also, the number of drugs approved per billion of spending has decreased to half per year, since the 1950s. Here, the DDCs present a modest risk, low cost, ambitious reward route to better and advanced medicines. It can assist in upgrading the different aspects like its physicochemical and its biopharmaceutical properties, by adding suitable drug co-formers, without much modification chemically.

It also helps against disadvantages like FDCs and treats additional indications by drug-drug interactions along with modified physicochemical attributes of every API. Whereas, speaking about regulations followed, the FDA first published instructions on the categorization of co-crystals in the year 2013, which was released in the Guidance in February in 2018 [67]. In the European Medicines Agency (EMA), a reflective document was released which distinguished pharmaceutical co-crystals in a familiar way [68]. There are hopes that these regulations and guidelines would strengthen the progress of the DDC market. On the other hand, a DDC can consist of an exclusive patent which means new exclusivity will enhance the commercial value of the products manufactured in the industry.

However, it will have to face certain obstacles in developing the DDC. The most prominent one being the designing and analysis of DDCs. From the DDCs mentioned above, it also is asserted that the majority of DDCs were mainly focused on identification of hydrogen-bonding techniques, emphasising the responsibility of intermolecular interactions. The DDCs were always designed on the basis of its molecular structure under direct influence of high throughput co-crystal screening. However, it depicts no guarantee that the synthesised DDCs are pharmaceutically accepted, which provides beneficial effects. Example given, Tomita and other researchers produced a DDC of theophylline-phenobarbital in the ratio of 2:1 [69]. Theophylline, an antiasthmatic, whereas phenobarbital which is known as a nervous system depressant. Such extreme combinations have no supporting proof for synergism or practical applications in therapy. Hence, it might not provide any therapeutic benefits. If we prepare DDCs from synergism or from practical applications, the structured DDCs are harder to be prepared. The other challenge is dosage formulation.

As co-crystals always have a mixed stoichiometric ratio, like 2:1, 1:1 or 1:2 and the oral dosage is advised in a suitable range. Hence, the fraction of a DDC might not align with the clinical requirements [70]. For example, Desirajusynthesised a DDC of lamivudine and zidovudine. These both are API which are antiviral agents, which might not be beneficial for developing drugs. But the mass ratio of lamivudine and zidovudine (1:1:2) differs from that of the dosage orally. This factor makes it difficult in clinical usage.

FUTURE PROSPECTS

From the DDCs mentioned above, it can be noted that although various pharmaceutically designed co-crystals are prepared, drug-to-drug co-crystals are rare. The reason behind this maybe selection of correct drug combinations for processing drugs is tough, because of various underlying factors like consideration, inclusion, and differential solubility, molecular interaction, packing patterns, dosage compatibility, therapeutic applications and drug to drug interactions. Also, along with all of this, the marketed APIs are very less, and so are the drugs to drug combinations. This can be solved by making efforts in three aspects, namely

1. The co-crystallization technique should be selected very carefully as its nature; Properties and morphology of co-crystals are influenced under this procedure.
2. Selection of suitable co-crystal formation methods and development of more effective Screening processes may gain an increase in the success rate of DDCs formulation.
3. Also, two different compounds always form more than a single crystal with different stoichiometric ratios. Thus, it becomes very important to explore DDCs with varied
stoichiometric ratios.
4. Nextly, the reach of DDCs to drug-nutraceutical co-crystals can be advantageous and thus, easier in developing. Numerous clinical trials confirm the potential benefits of different nutraceuticals in various disorders [71-73].

However, the maximum number of nutraceuticals are weak ionizing agents which showcase extremely low solubility and bioavailability [74]. Thus, it limits the clinical trials of nutraceuticals in clinical applications. Drugs with higher solubility enhance the extent of absorption of nutraceuticals and modulates the physicochemical properties and thus provides drug to drug synergism for the marketed APIs. This also can result in the occurrence of an entirely new range of safer and more effective combinations, which prove to

be a therapeutic amalgamation of APIs and nutraceuticals with increased synergistic benefits and reduced ill effects.

ADVANCEMENT OF CO-CRYSTALS PREPARATION

Freeze drying

Freeze enhanced drying, also called Lyophilization, is also a type of process used in manufacturing of pharmaceutical co-crystals. In the last few years, multiple attempts are made for inculcating this process post its recognition in certain applications in fields like biotechnology, pharmaceutical, diagnostics, food industries, etc. this process consists of various steps through drying the components, freezing of the wet substance. It is then sublimated directly into the vapour state by applying a low and partial pressure of water vapour. Scientists like Eddleston and other scientists in the year 2013 used this as the chief method for production of new solid formations of pharmaceutical co-crystals [76]. Various co-crystals systems were diluted in water or can also be done in t-butanol, or a novel solution containing caffeine which includes Theophylline and other new co-crystals form of Theophylline: oxalic acid. They cause them to co-crystallize in different forms. The diffraction of x-ray powder and the DSC analysis indicate pentahydrate 2:1 Theophylline and cocrystals of oxalic acid for the freeze and dry specimens were present. The Theophylline-caffeine samples also showed similar characteristics to the form one co-crystals, however, the amorphous halo and reflections were absent. More studies about it suggest the emergence of a single N-H Nitrogen and Hydrogen bond amongst the molecules. Thus, it can be concluded that drying helps in forming the co-crystals through an amorphous phase which develops in solvent sublimes.

Microfluidic and the jet dispensing technique

Microfluidic is a technique which facilitates trial to be held at higher throughput by the channel of running numerous samples in a second and under controlled fluids in a network of micrometer sized channels [77-78]. The microfluidic and the jet are used in different fields like diagnostic, biological studies, drug discovery, pharmaceutical crystallization, and molecular genetics. A new proposed approach depending on this procedure was developed by Goyal and researchers in the year 2012 [79-80]. In the particular method, the solutions that are saturated from the parent compound and co-formers are made to be dissolved in different solutions in small quantities, likely 240µg/ 48 conditions, for one chip approximately 90nL per chamber using combinatorial mixing. On application of a dual two-phase screening, caffeine was synthesized with a broad spectrum of conformer and varied solvents for identification of combination with highest level of propensity for the process of co-crystallization. The main compound, caffeine was put vertically, through into the chips, whereas the co-formers horizontally. The first screening disclosed the process of forming the co-crystals in as many as 82/288 conditions. This phenomenon can be due to these underlying reasons-

1. The span of time required i.e. 12 to 72 hours.
2. The differences showcased in the method used for mixing.
3. Inadequate amount of the original compound and
4. Incorrect formulation of the pharmaceutical co-crystals.

In the next round, the same process was repeated with the pairs consisting of highest propensity from the first round. The results suggested that this screening of the co-crystals that were formed, using the microfluidic chips, is trustworthy and generates results. Of the many advantages was also the line coupling factor of a Raman probe for studies of the thus formed co-crystals.

Ultrasound co-crystallization

Ultrasound co-crystallization, also known by the name of sonocrystallization,, too is a liquid assisted machinery. This is developed for studying the varied co-crystals. This was first used by Childs and others involved, in the year 2007. Where he used the method of sonic slurry for developing co-crystals with different drugs - conformer pairs. In some experiments, sonication was performed for 24 hours on seeded and unseeded slurries of crystal [81]. Further, renowned researchers Bucar and scientists like MacGillivray used ultrasound radiation, in very low radiation, for developing nanostructured non pharmaceutically manufactured co-crystals of resorcinol and of 4, 4'-bpe. With the assistance of an ultrasound bath, ultrasonic radiation was passed through an ethanol suspension of the 2 compounds at 5C for 180 minutes [82]. As per the discussion, this process consists of formation, growth and collapse of the bubbles inside the micro scale, due to intensive heat and pressure. Due to cavitation, shear forces and crystal fragmentation are noted, increasing the speed of nucleation and crystallization but also decreases the speed of super saturation in vicinage of the bubbles.

CONCLUSION

In this particular review, we analyse the different technology advancements in experimental screening and in production of pharmaceutically synthesized co-crystals for overcoming the flaws in the aspects of its

physical attributes of the APIs. The recent advancements in synthesized co-crystals, has led to better quality of drugs. Additionally, several new ways have been invented which have the potential of producing good results, however only a selected few showcased a high throughput co-crystals production having the required specifications. Co-crystals can also be formulated for commercial use as APIs. They form an effective alternative choice for developing the drugs which furthermore enhance the solubility of the co-crystals, bioavailability of the crystals, stability, and process ability. But there is the presence of varied obstacles like selection of conformers, and physicochemical characterization. Conscious drug co-formers screening and formulation results in successful co-crystal manufacture. We also assess the co-crystals through standard analysis like the spectroscopic analysis, terahertz spectroscopy, solid state nuclear magnetic resonance, through thermal gravimetry method amongst the many.

LIST OF ABBRIVATIONS

TGA: - Thermal gravimetric analysis
DSC: - Differential scanning calorimetry
PVP: - Polyvinylpyrrolidone
PXRD: - Powder X-ray diffraction
EMA: - European Medicines Agency

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise

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