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Emerging Trends In Cocrystallization: Screening, Formulation, And Characterization Techniques

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ABSTRACT: *Recent advancements in co-crystallization methods have revolutionized the pharmaceutical industry by enhancing the stability, solubility, and other physicochemical properties of existing drug compounds, without compromising their chemical and pharmacological integrity. Co-crystals represent an innovative approach to improving drug formulations, leveraging old drug entities to achieve superior therapeutic outcomes.*

One notable advancement lies in the formulation techniques themselves, such as electrospray and laser-irradiation methods. These methods enable solvent-free co-crystallization, offering higher yields and minimizing material loss, thereby making the process more efficient and environmentally friendly.

Screening methods for co-formers have also evolved significantly, transitioning from traditional trial-and-error approaches to sophisticated in-silico methods. This transformation accelerates the screening process, expanding the pool of potential co-formers while reducing the time required for selection.

Advanced evaluation techniques, including Raman spectroscopy and solid-state NMR spectroscopy, have emerged as indispensable tools for characterizing co-crystals. These methods provide detailed insights into the crystal lattice structure and elucidate the interactions between drug and co-former molecules. Moreover, they distinguish between the formation of salts and co-crystals, ensuring precise characterization and understanding of the resulting formulations.

Co-crystals not only rejuvenate existing drug molecules but also facilitate the development of entirely new formulations. They represent a promising avenue for pharmaceutical research, offering vast opportunities to optimize drug properties and achieve previously unattainable improvements. In essence, co-crystals embody the ethos of "making a good drug better," propelling pharmaceutical innovation forward and opening new frontiers in drug formulation and enhancement.

Keywords: *Co-crystals, Screening of conformer, COSMO-RS, PXRD study, Raman spectroscopy, DSC study, SSNMR study.*

1. INTRODUCTION:

In the pharmaceutical industry, a significant number of newly developed drug entities face challenges such as poor solubility and unfavorable physicochemical properties like flowability, hygroscopicity, particle size, crystal lattice, density, taste, and thermal stability [1,2]. These issues not only hinder formulation efforts but also impact the efficacy and safety of medications. Over 40% of marketed drugs and more than 60% of new drug entities exhibit poor aqueous solubility due to their large molecular size and lipophilic nature [2,3]. Additionally, patent expirations and subsequent revenue loss from generic competition pose substantial economic challenges for pharmaceutical companies, necessitating innovative solutions to extend patent protection and improve drug formulations [4].

To address these complexities, researchers are exploring methods to modify existing drug molecules while maintaining their pharmacological effectiveness and enhancing their physicochemical properties. Techniques such as salification and co-crystallization have emerged as promising strategies for achieving these goals. These methods involve combining active pharmaceutical ingredients (APIs) with excipients or other APIs in novel solid lattice forms, including salts, solvates/hydrates, polymorphs, and co-crystals [5]. Each form may exhibit distinct pharmaceutical properties, underscoring the importance of thorough screening and characterization during drug development [6].

Among these approaches, co-crystallization stands out as a particularly impactful advancement. Unlike salts, co-crystals do not rely on ionic bonds for formation and can involve non-ionizable molecules, provided the co-formers are safe for human consumption [2,11]. Co-crystals offer advantages in terms of intellectual property rights and commercial viability, leveraging existing data from previous pharmaceutical products to facilitate patent approvals [2,12]. Although co-crystals have yet to achieve widespread market adoption, they hold immense promise for future pharmaceutical innovations.

Various methods can be employed to formulate co-crystals, including neat grinding, liquid-assisted grinding, cooling crystallization, solvent evaporation, fusion, anti-solvent addition precipitation, supercritical fluid technology, ultrasound-assisted solution crystallization, electrospray, and spray congealing. The selection of an appropriate co-former is crucial in co-crystal formation and can be facilitated through computational tools such as Cosmologic®, which assesses the enthalpy differences between pure drug, pure co-former, and their mixture to predict co-crystal formation feasibility [13,14].

Characterization of co-crystals is essential for confirming their structure and properties. Techniques like single crystal/powder X-ray diffraction, differential scanning calorimetry, hot stage microscopy, and spectroscopy (Raman, IR, solid-state NMR) are commonly used for this purpose. Powder X-ray diffraction is particularly reliable for confirming co-crystallization, while Raman spectroscopy aids in identifying and distinguishing pure drug, co-former, and co-crystal components based on their spectral signatures.

In conclusion, this review comprehensively discusses the various types of co-crystals, methods for their formulation, co-former selection strategies, characterization techniques, and the utility of essential software in co-crystallization studies. By advancing our understanding and application of co-crystallization, researchers aim to overcome the challenges posed by poorly soluble drug molecules and pave the way for more effective and commercially viable pharmaceutical products.

2. Definition:

2.1. Co-crystals:

According to the USFDA, co-crystals are crystalline substances composed of two or more distinct molecules, where one molecule is the active pharmaceutical ingredient (API). These molecules are present in a specific stoichiometric ratio within the crystal lattice, bound together by non-ionic and non-covalent interactions [15]. This definition highlights co-crystals as a structured form of pharmaceutical material that integrates multiple components into a single crystalline entity, facilitating enhanced properties and applications in drug formulation and development.

2.2. CO-FORMER:

According to the USFDA, a co-former is described as a component that interacts non-ionically within the crystal lattice of the active pharmaceutical ingredient (API). Importantly, a co-former is not considered a solvent (including water) and is typically characterized as non-volatile [15]. This definition underscores the role of co-formers in co-crystal formation, where they contribute to the structural integrity of the crystalline material alongside the API, facilitating improvements in drug stability, solubility, and other physicochemical properties.

3. Method for co-crystallization:

Co-crystallization methods can be broadly categorized into two main types: solid-state co-crystallization and liquid (solution) co-crystallization. In solid-state co-crystallization, the neat/dry grinding method utilizes sheer force to facilitate the formation of co-crystals. This method can be modified to liquid-assisted grinding by adding a small amount of solvent. Alternatively, in solution crystallization, an excess of solvent is used to dissolve the components (active pharmaceutical ingredients and co-formers), with co-crystals precipitating in the anti-solvent addition method or forming as dry residue through solvent evaporation and cooling crystallization. Another approach is fusion co-crystallization, where a physical mixture of the active pharmaceutical ingredient(s) and co-former(s) is heated until melted and then cooled to obtain a fused, single material as co-crystals. Novel methods for co-crystallization include spray drying, microwave-assisted co-crystallization, supercritical fluid technology, ultrasound and ultrasound-assisted solution crystallization, electrospray method, laser irradiation, and spray congealing method. These advanced

techniques offer diverse means to achieve co-crystal formation, each with unique advantages in terms of efficiency, yield, and control over crystal properties.

3.1. CO-CRYSTALS BY GRINDING:

3.1.1. NEAT GRINDING:

Neat grinding is a solvent-free method used to form co-crystals by manually pressing and crushing a physical mixture of materials in a stoichiometric ratio, typically in a mortar and pestle or mechanically using devices like ball mills or vibrational mills. This process relies on size reduction to promote surface interactions between co-crystal components, facilitating the formation of covalent bonds or supramolecular reactivity between the target molecule and co-former. Neat grinding serves as a practical alternative to solvent-based co-crystallization techniques and has demonstrated superior selectivity in some cases. The typical grinding time ranges from 30 minutes to 1 hour, making it a straightforward, rapid, and efficient method for co-crystal synthesis [5,16].

For instance, Yuta Otsuka and colleagues successfully produced co-crystals of caffeine and oxalic acid using the neat grinding method. Their study highlighted that rotational speed during grinding is more critical than temperature in achieving chemical equilibrium and enhancing co-crystal content. Increasing rotational speed was found to correlate with higher yields of co-crystals [17].

3.1.2. Liquid assisted grinding (lag):

Liquid-assisted grinding (LAG) represents a refinement of the neat grinding method, involving the addition of a small amount of solvent to aid in the formation of co-crystals. Unlike neat grinding, where no solvent is used, LAG utilizes a minimal quantity of solvent that only persists for the duration of the grinding process. The solvent acts as a catalyst, facilitating co-crystallization by wetting the surfaces of the co-crystal components and enhancing the efficiency of the process [18].

An example of successful application of LAG is demonstrated by Fang Liu and colleagues, who synthesized co-crystals of isoniazid using this method. Their study focused on isoniazid-syringic acid co-crystals, which showed promising results in mitigating the hepatotoxicity associated with isoniazid in rat hepatotoxicity studies. These co-crystals also exhibited a sustained release mechanism, allowing for the gradual release of isoniazid. Syringic acid, known for its poor solubility and bioavailability, benefitted from improved solubility in the co-crystal system compared to physical mixtures of the components, contributing to the sustained drug release observed in vitro [19].

In another study, Terence J. Noonan and co-workers successfully synthesized three different co-crystals of imidazopyridine drug leads (MMV) with adipic acid, fumaric acid, and glutaric acid co-formers using LAG. Confirmation of co-crystal formation was achieved through techniques such as powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). Their kinetic solubility study demonstrated enhanced solubility for all three co-crystals compared to untreated MMV. Additionally, the drug release profiles varied among the co-crystals, with MMV-ADI (2:1) showing a sustained release pattern, while MMV-GLUT (1:1) and MMV-FUM (2:1) exhibited both sustained and burst release patterns. The study also highlighted the utility of melting point determination for screening eutectic mixtures, salts, and co-crystal products [20].

3.2. Co-crystals by solvent evaporation method:

In the solvent evaporation method of co-crystal formation, an excess of solvent is employed to dissolve the drug and co-former in their stoichiometric ratio. The solvent is then removed either at room temperature or under vacuum to expedite drying [21–23]. This method is commonly used to produce single crystals of multi-component systems for characterization using single-crystal X-ray diffraction. Despite its advantages in providing high-quality and pure co-crystals suitable for lab-scale preparation without requiring expensive equipment, the solvent evaporation method has drawbacks such as the use of large amounts of solvent and limited scalability [24,25,26].

For example, Wen Li and colleagues utilized the solvent evaporation method to prepare co-crystals of baicalein with theophylline. The resulting co-crystal demonstrated significant improvements in both in vitro and in vivo evaluations [26]. Similarly, Jos´e Venancio ˆ Chaves Júnior and co-workers employed rapid solvent evaporation to prepare ferulic acid-nicotinamide co-crystals, which exhibited a 70% increase

in ferulic acid solubility and enhanced dissolution properties at pH 6.8 compared to physical mixtures [27]. These studies underscore the effectiveness of the solvent evaporation method in enhancing the pharmaceutical properties of co-crystals through controlled crystallization processes.

3.3. co-crystals by anti-solvent addition crystallization:

The anti-solvent addition method for co-crystal formation involves dissolving the components of the co-crystal in a suitable solvent until complete solubilization is achieved. Subsequently, an anti-solvent, which is miscible with the solvent, is added to induce precipitation of the co-crystals. The selection of appropriate solvent and anti-solvent pairs is crucial in this method, ensuring that the solvent can effectively dissolve both the drug and co-former components [28–30].

For instance, In-Chun Wang and colleagues utilized the anti-solvent addition method to produce carbamazepine-saccharine co-crystals. They optimized the ratio of drug and co-former under specific conditions to achieve optimal purity and crystal quality. Their study emphasized the critical role of solvent and anti-solvent selection, as well as the precise ratio of co-crystal components, in successfully forming co-crystals using this method [31]. This approach highlights how careful consideration of solvent properties and conditions can influence the outcome and quality of co-crystals, impacting their pharmaceutical characteristics and applications.

3.4. Co-crystals by cooling crystallization:

In the cooling crystallization method, the process begins with heating the solution to dissolve the co-crystal components, followed by allowing the solution to stabilize. Once stable, the temperature is gradually reduced at a controlled rate (typically measured in degrees Celsius per minute) to induce the formation of co-crystals within the solution. The crystallized product is then collected using vacuum filtration. The specific temperature for heating varies depending on the solvent and the nature of the co-crystal components [32].

Nan Hee Chun and colleagues illustrated the efficacy of cooling crystallization in forming indomethacin-saccharin (IMC-SAC) co-crystals. In their study, the solution was initially heated to 45°C and allowed to settle for 30 minutes. Subsequently, the temperature was decreased at a rate of 1°C per minute using a cooling circulator until reaching 15°C. This approach was designed to evaluate the synergistic effect of combining cooling crystallization with the anti-solvent method, which enhances the degree of supersaturation in the solution. This higher supersaturation level promotes the growth of co-crystals through nucleation of pure IMC-SAC without dissolution or transformation, resulting in improved yield and crystallinity of the co-crystal products [33]. This method underscores the strategic combination of process parameters to optimize co-crystal formation and quality in pharmaceutical applications.

3.5. Co-crystals by fusion method:

In the hot-melt method of co-crystal formation, the drug and co-former are either melted separately or in a physical mixture, ensuring uniform mixing to achieve a homogeneous blend of components. The melted mass is then allowed to cool down at room temperature, leading to the solid-state formation of co-crystals. Alternatively, hot-melt extrusion can be employed for co-crystallization, where materials are melted and mixed using a heated screw extruder.

This method offers several advantages over solvent-based techniques, including continuous processing, elimination of solvent use, rapid operation, reduced material waste, and high conversion efficiency [34,35]. However, a limitation of hot-melt extrusion is its unsuitability for heat-sensitive materials.

For example, P. Barmpalexis and colleagues conducted a study where they formulated co-crystals of carbamazepine-nicotinamide and ibuprofen-nicotinamide using soluplus (SOL) as a matrix polymer via melt mixing. The co-crystals with soluplus were prepared by heating the mixture at 170°C for CBZ/NCT-SOL and 140°C for IBU/NCT SOL until a homogeneous blend was achieved using mortar and pestle. Cooling the melted samples resulted in crystal formation at higher concentrations of active pharmaceutical ingredient (API) and co-former, whereas lower concentration samples remained amorphous. This outcome was attributed to soluplus acting as a kinetic barrier to drug recrystallization [34]. This approach highlights the utility of melt mixing techniques in enhancing the stability and performance of co-crystal formulations.

3.6. Co-crystals by spray drying:

Spray drying is a continuous and scalable process used to convert liquid solutions or suspensions into solid powders using specialized spray dryer equipment. This method is particularly advantageous for preparing pure co-crystals from both congruent and incongruent saturating solutions. However, it requires expensive equipment that demands high maintenance and skilled operation. Spray drying is especially suitable for formulating amorphous solids, although it can pose challenges in producing crystalline phases from co-crystal components [36,37].

For instance, David Walsh and colleagues utilized the spray-drying method to prepare sulfadimidine 4-aminosalicylic acid co-crystals. Their study underscored the critical role of spray drying parameters such as flow rate and heating temperature in achieving high-quality drug co-crystals [38]. This research highlights the importance of meticulous control over process variables to optimize the formation and quality of co-crystals using spray drying technology.

3.7. Co-crystals by supercritical fluid technology:

Supercritical fluid technology offers distinct advantages over conventional co-crystallization methods, including its environmentally friendly nature, elimination of drying steps, absence of residual solvents in final products, production of micro-sized particles, and suitability for continuous processing [39]. Over recent years, various modifications of supercritical fluid technology have emerged, such as rapid expansion of supercritical solution (RESS), supercritical anti-solvent crystallization, supercritical fluid enhanced atomization (SEA), atomization, and gas anti-solvent crystallization (GAS), each detailed comprehensively in the review by Concepeion Pando et al. [40].

For example, Marcela M. Ribas and colleagues utilized supercritical fluid technology to prepare high-purity co-crystals of curcumin-N-Acetylcysteine, highlighting the method's capability to produce co-crystals of superior quality [41]. Napada Wichianphong and co-workers successfully synthesized mefenamic acid-nicotinamide co-crystals using the gas anti-solvent method, emphasizing the critical influence of drug-co-former ratio and drug saturation percentage on co-crystal dissolution rates [41]. Additionally, Luis Padrela and co-workers demonstrated the potential of supercritical fluid technology in screening and formulating co-crystals of various drugs, achieving particle sizes ranging from 0.3 to 10 μm [42].

These studies underscore the versatility and efficacy of supercritical fluid technology in advancing co-crystal research and development, offering promising prospects for enhancing pharmaceutical formulations through precise control over particle size and purity.

3.8. CO-CRYSTALS BY ULTRASOUND-ASSISTED SOLUTION CRYSTALLIZATION:

Ultrasound-assisted solution crystallization (USSC) utilizes ultrasound waves to induce nucleation during the crystallization process of drugs. This method exploits ultrasound to create voids or air bubbles within the liquid, which undergo cycles of compression and rarefaction. During compression, these bubbles absorb energy and violently collapse, thereby releasing energy that elevates the local temperature of the liquid. This phenomenon facilitates the compression of air bubble contents, promoting the formation of co-crystals from a homogeneous solution of co-crystal components [43].

Suyog Aher and colleagues successfully synthesized caffeine-maleic acid co-crystals using USSC. Their study demonstrated that USSC effectively altered the supersaturation conditions of the components in the liquid, thereby facilitating the nucleation and growth of co-crystals [44]. Similarly, Prafulla Apshingekar and co-workers employed a green USSC method in an aqueous medium to produce caffeine-maleic acid co-crystals. They highlighted USSC's ability to mitigate the non-congruency of components and enhance the solubilization of co-crystal components in the aqueous medium. Specifically, the solubility of caffeine increased from 0.104 ± 0.011 to 0.642 ± 0.071 μmol/ml, while that of maleic acid increased from 3.448 ± 0.299 to 7.327 ± 0.613 μmol/ml due to the ultrasound pulses [45].

Moreover, the study emphasized that ultrasound in an aqueous solution could narrow the co-crystallization region in the ternary phase diagram for caffeine-maleic acid (1:1) co-crystals. However, co-crystals with a ratio of 2:1 exhibited a broader region in the phase diagram but displayed poorer stability, likely due to the significant difference in solubility between the components in the solvent used, leading to dissociation into individual components [45].

In summary, ultrasound-assisted solution crystallization presents a promising approach for enhancing solubility and facilitating the formation of co-crystals, particularly in aqueous environments.

3.9. CO-CRYSTALS BY MICROWAVE-ASSISTED CO-CRYSTALLIZATION:

Microwave-assisted co-crystallization is recognized for its efficiency, cost-effectiveness, speed, and scalability. Unlike conventional heating methods, it accelerates the rate of co-crystal formation significantly, thereby reducing reaction times and enhancing yields. In this method, co-crystal components and solvents are placed in a microwave radiation reactor at appropriate temperatures and pressures for a specified duration to produce the desired co-crystal product [46].

Dipali Ahuja and colleagues exemplified this approach by synthesizing sulfamethazine co-crystals using microwave-assisted co-crystallization. Their research underscored that microwave radiation as a heating source expedites co-crystal formation compared to traditional heating methods. Importantly, the study demonstrated the scalability of this technique, achieving production capacities ranging from 0.2 to 20 grams without compromising product quality [47]. These advantages make microwave-assisted co-crystallization particularly valuable in industrial settings, enabling faster formulation processes and ensuring high-quality product outcomes.

3.10. CO-CRYSTALS BY ELECTROSPRAY METHOD:

Electrospray is a method that concurrently generates droplets and electric charges on them. In this process, a solution containing co-crystal components is sprayed through a capillary nozzle under a high electric potential. This electric field elongates the droplets into a jet, which subsequently dries to form powder particles. These particles are then collected by a charged particle collector. Figure 1 illustrates the step-by-step process of electro spraying and co-crystal formation in the electrospray method [48].

Sharvil Patil and collaborators explored the potential of electrospray for formulating co-crystals, particularly demonstrating significant advantages for Forskolin-nicotinamide co-crystals. They observed a substantial reduction in particle size compared to pure Forskolin, along with a 2.74-fold increase in solubility compared to Forskolin alone. This study highlighted that the needle-shaped co-crystals produced by the electrospray method offer a larger surface area, thereby enhancing dissolution rates compared to co-crystals obtained through other methods [48].

In another study, Shahram Emami and colleagues utilized electrospray to formulate naproxen-nicotinamide co-crystals in ratios of 2:1, 1:1, and 1:2. They found that only the 2:1 ratio of NPX-NIC co-crystals could be successfully formulated with high purity. Other ratios resulted in products containing higher impurity levels. The timing of particle collection significantly influenced the conversion of amorphous forms to crystalline forms: immediate collection after processing retained some amorphous content, while collection after 24 hours showed complete conversion to crystalline form. Optimal conditions such as the working distance of 20 cm and the collection time were crucial for achieving high-quality co-crystals [49].

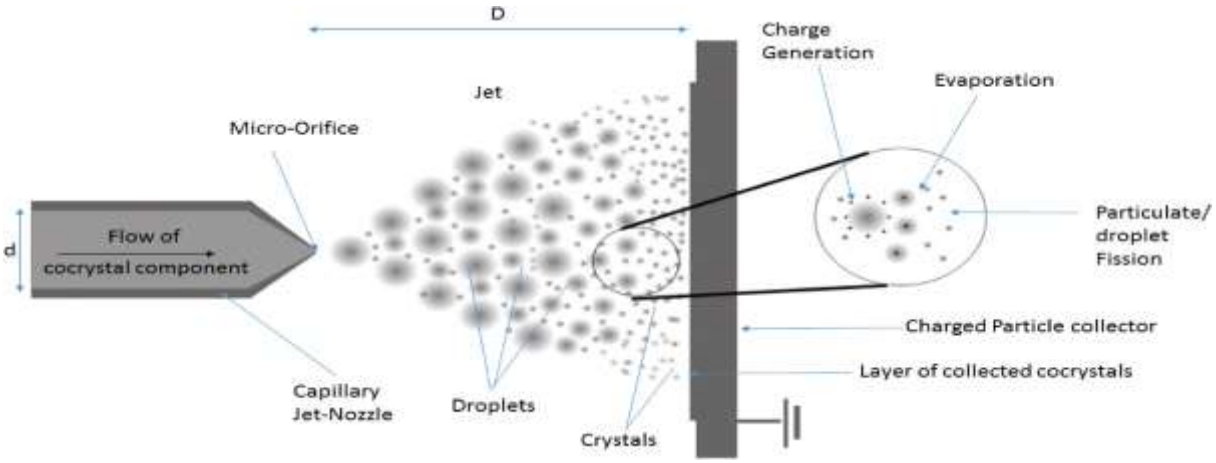

Fig. 1. Electrospray cocrystal formulation mechanism.

3.11. Co-crystals by laser irradiation:

As depicted in Fig. 2, the laser irradiation method involves exposing a physical mixture of co-crystal components to intense radiation energy for a brief duration. This rapid exposure causes a rapid increase in temperature, leading to the melting of the co-crystal components. Subsequently, the mixture is allowed to cool, promoting recrystallization into co-crystals. For this technique to be effective, the co-former ideally should be a sublime material, facilitating nucleation through the vapor phase, which is a plausible mechanism for formulation [50].

Varin Titapiwatanakun and colleagues showcased the efficacy of laser irradiation in synthesizing caffeine-oxalic acid (2:1) co-crystals. Their experiment utilized a CO2 laser to deliver radiation energy to the co-crystal components. The study highlighted that the speed and power settings of the laser are crucial factors influencing the production of high-quality co-crystals. Insufficient laser power fails to attain the necessary temperature for component melting, while excessive power risks degradation of the co-crystal components. During their investigation, the laser settings were optimized within the range of 50–60 percent of the maximum achievable value by the instrument [51].

3.12. Co-crystal by spray congealing:

Spray congealing is a solvent-free green method for the synthesis of co-crystals. A stoichiometric mixture of co-crystal components is melted in a beaker and spray congealing is performed by a modified two-nozzle spray dryer. Schematic diagram in Fig. 3 shows flow of liquid material through instrument. A spray dryer is used for the atomization of melted mass. Solidification is favored by a concurrent stream of nitrogen and solid co-crystals are collected from the cyclone separator [52]. ´Iris Duarte and co-workers demonstrated the potential of spray congealing in the formulation of caffeine-salicylic acid co-crystals. The obtained co-crystals were compact and spherical. Co-crystals adhered to each other in aggregate form. In this study, it is observed that in situ adjustments of co-crystal properties like purity, shape, size, and flow properties can be done by varying the temperature difference (◦C) and feed atomization rate (L/min) [53].

4. CO-FORMER SELECTION METHODS:

Co-former selection is a very crucial and critical step in the formation of Co-crystals [54,55]. Changes in the physicochemical properties of co-crystals depend upon the suitability of the co-former. Appropriate selection of co-formers improves the physicochemical properties of co-crystals and also a biased selection of co-formers can worsen the same.

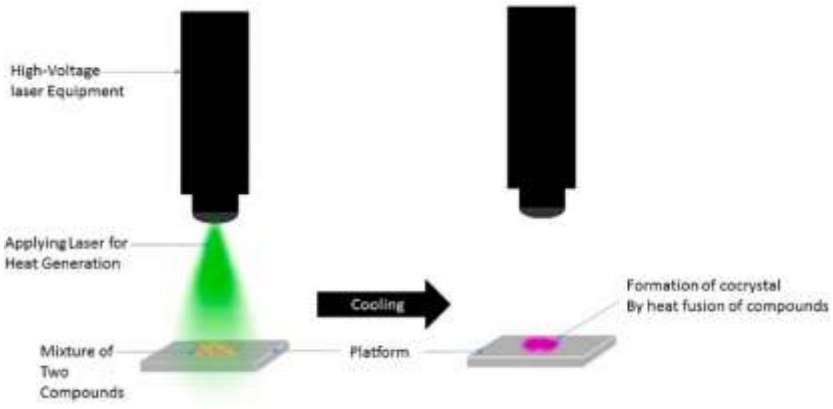

Fig. 2. Co-crystals by laser irradiation.

The drug-to-co-former ratio also affects the physicochemical properties of final co-crystals [56]. Therefore, various selection methods are used to screen out suitable co-formers for specific drug molecules [57]. There are seven different methods currently available for preliminary screening of co-formers.

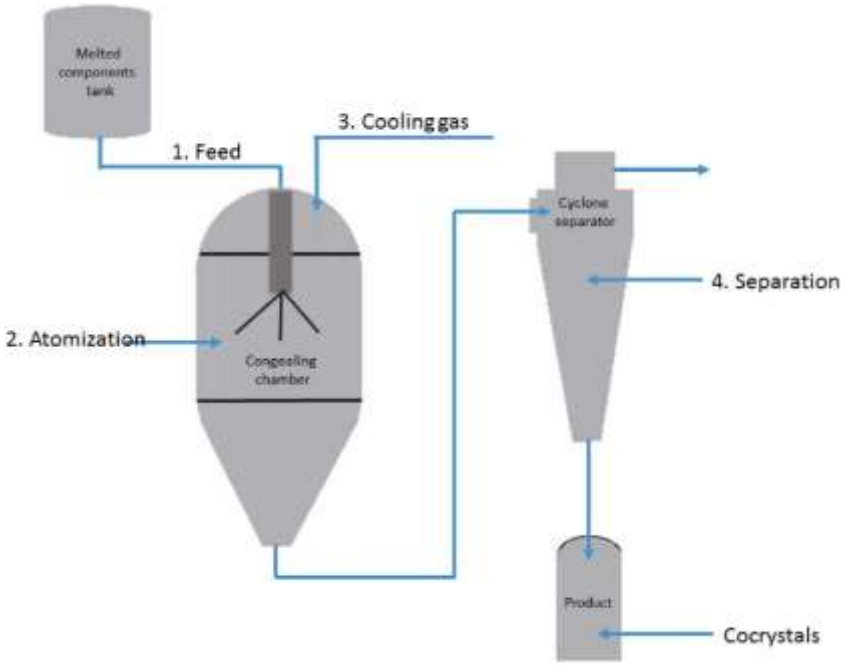

Fig. 3. Spray congealing instrument (spray dryer).

4.1. PKA BASED MODEL:

The formation of co-crystals hinges on the transfer of protons between acidic and basic functional groups present in their components [58]. Predicting the potential for co-crystal or salt formation involves calculating the ΔpKa value. This metric quantifies the difference in pKa values between acid and base pairs within the co-crystal components. A linear relationship has been established between ΔpKa and the probability of proton transfer, particularly in crystalline complexes where ΔpKa ranges between -1 and 4. For co-crystal formation, ΔpKa values ideally fall between 0 and 3 [59].

In a study led by Mehta et al. on ketoconazole, co-crystals (KTZ:PHBA) were formed with para-hydroxybenzoic acid, which has a ΔpKa of -1.6. This study underscores that co-crystal formation is feasible even with a negative ΔpKa value [60]. The European Medicines Agency recognizes ketoconazole as a dibasic agent with pKa values of 2.94 and 6.51. The ΔpKa value of -1.6 corresponds to the first pKa value, which falls within the favorable range of 0-3 for co-crystal formation [61]. Mehta et al. further concluded from their in vitro studies that para-hydroxybenzoic acid exhibits hepatoprotective properties, reducing the hepatotoxic effects associated with ketoconazole. Their research demonstrated improved antifungal activity of the KTZ:PHBA co-crystal compared to ketoconazole and para-hydroxybenzoic acid alone [60].

4.2. Cambridge structural database:

Cambridge structural database is a computer-based approach for the determination of appropriate co-crystals forming pairs, reducing time for screening and reducing the cost of experiments. Cambridge structural database facilitates the statistical analysis of packing characteristics and provides info about general functional groups. Cambridge structural database is a validated tool for the selection of co-formers. In this [62] In CSD, a new network approach is utilized to gain a better understanding of co-formers which combine successfully to target molecules for the formation of co-crystals. Devogelaer et al. have developed an algorithm for screening of drug and co-former, which are suitable for forming inter molecular weak bonding. The algorithm finds an appropriate co-former from a cluster of selected co-formers which are already been screened by co-former degree k. In this selection module, Devogelaer et al. have selected two types of network approaches, monopartite and bipartite. Monopartite network approach will show results related derived from local community links and bipartite network approach will show results regarding two different molecules (common neighbor) interaction possibilities. A miX

method, mono-bipartile method can be also used for finding simillar kind of

interaction between molecules, which can be helpful for determining the final possibility of crystal arrangement and sequencing of API and co-former in crystal lattice [63].

4.3. Hydrogen bonding:

In co-crystal formation, non-covalent bonds like hydrogen bonds and van der Waals forces are responsible for the interaction between the target molecule and co-former. Among these forces, hydrogen bonding plays a major role in the formation of co-crystals [64,65]. Hydrogen bond propensity (HBP) and hydrogen bond energy (HBE) are knowledge-based prediction tools for the selection of co-formers. HBP is the probability of specific hydrogen bond formation which depends on the structural characteristics of the specific functional group. ΔHBP is calculated by the following equation [66].

ΔHBP–(HBP API—COFORMER - HBP API—API/COFORMER—COFORMER) (1)

If ΔHBP value is positive then co-crystal formation is possible among selected components and if the value is negative then co- crystal formation is not possible.

For HBE, it is calculated by using molecular electrostatic potential using density functional theory (DFT) ΔHBE is calculated by the following question.

ΔHBE = (HBE API—COFORMER - HBE API—API/COFORMER—COFORMER)(2)

If ΔHBE value is positive then co-crystal formation is possible and if negative then co-crystal formation is not possible among co- crystal components [66].

Although HBP provide best results regarding the prediction of co-crystal formation, the accuracy of method is low, when used alone. With other methodologies like molecular complementarity (MC), and hydrogen-bond energy (HBE), the accuracy of result can be improved [66].

4.4. Supramolecular synthon approach:

As per the supramolecular synthon approach, the functional group present in target molecules and co-formers has a significant role in the synthesis of co-crystals [67,68]. A suitable functional group from the co-former is used for a specific target molecule functional group. Synthons are available as basic structural units in supramolecular, which are associated with non-covalent bonding. The supramolecular synthon approach is classified into two classes, homosynthon, and heterosynthon. Homosynthons are composed of the same functional group as in co-former and target molecules. Heterosynthons are composed of two different functional groups one in the co-former and the other in the target molecule. Generally, homosynthons are less favored than heterosynthons [69].

Tejender S. Thakur and co-workers predicted the crystal structure of 2 methyl benzoic acid-2 amino 4 methyl pyrimidine co-crystals by using the supramolecular synthon approach. The study suggests the supramolecular synthon approach provides useful structural insight and increases the success rate of crystal structure prediction. It is a robust method in thermodynamic system applicability [70].

4.5. Hansen solubility parameter:

Hansen solubility parameter is an important method for measurement of the target molecule and co-former miscibility for multi- component systems like co-crystals. Hansen's solubility parameter suggests that the success rate of co-crystal formation is increased with the improvement in the miscibility of two components in the system [69].

4.6. Cosmo-rs:

The COSMO-RS fluid phase computation of thermodynamics is used for accurate and very efficient virtual screening of co-formers for co-crystallization. The screening is based upon the excess enthalpy (H_{ex}) property, which describes the miscibility of the co-former with API in an amorphous (subcooled liquid) state [14]. The following equation is used for the calculation of excess enthalpy:

Hex = HAB - Xm HpureA - Xn HpureB (3)

Where H_{pure} and H_{AB} are molar enthalpies in pure and in mixture state with mole fraction of drug (m) and co-former (n).

Co-formers that have the highest chances of formation of co-crystals are determined by the lowest H_{ex} values [14,71,72].

The f_{fit} approach for screening co-crystals considers the flexibility of the target molecule and co-former by

the number of rotational bonds present in co-crystal components. For the calculation of F_{fit} following equation is used.

$F_{fit} \sim H_{mix} + a\ (\max(1, nrot_{API}) + \max(1, nrot_{COF})$ (4)

Where "a 0.5102" has been determined by a set of 300 target molecule co-former pairs from the literature. The kinetic nature of molecules provides more flexible components which may have a higher barrier for crystallization [14].

5. Characterization of Co-crystals:

Various methods are employed for the characterization of co-crystals, reflecting significant advancements in recent years. Key techniques include single crystal and powder X-ray diffraction (XRD & PXRD) [73], thermal analysis such as Differential Scanning Calorimetry (DSC) [74] and Hot Stage Microscopy [75], and spectroscopic methods like Fourier Transform Infrared Spectroscopy (FTIR) [77], Raman Spectroscopy [76], and Solid-state Nuclear Magnetic Resonance Spectroscopy (SSNMR) [77]. This review section provides a concise overview of these characterization technologies along with current examples that illustrate their application in co-crystal analysis.

5.1. x-ray diffraction method (xrd) and powder x-ray diffraction method (pxrd):

X-ray diffraction (XRD) is a crucial and accurate method for identifying and quantifying co-crystals. Single-crystal XRD is typically employed to determine the structure of large crystals, often obtained through methods like solvent evaporation. Co-crystals produced via grinding methods cannot be analyzed using single-crystal XRD and are instead characterized using powder X-ray diffraction (PXRD). PXRD is particularly useful for identifying co-crystal formations because it reveals changes in characteristic peaks compared to the individual components of the co-crystal. XRD techniques are also instrumental in determining the yield of co-crystals by quantifying the percentage of co-crystals and co-crystal components in the final product [73].

For instance, Geetha Bolla and colleagues utilized PXRD to elucidate the structure of acemetacin co-crystals, obtaining three-dimensional data crucial for understanding the crystal structure of acemetacin [78].

5.2. Thermal analysis method:

In thermal analysis, there are mainly two methods available to carry out the characterization of co-crystals.

5.2.1. Differential scanning calorimetry (dsc):

Differential scanning calorimetry (DSC) is a straightforward and convenient method widely used for characterizing co-crystals [79]. Co-crystals typically exhibit distinct changes in their endothermic and exothermic peaks compared to their pure components. The DSC peak of a co-crystal appears between those of its individual components, which serves as a key indicator used in screening co-crystals by comparing it with the DSC peak of the physical mixture of co-crystal components [80] [74,81]. However, it should be noted that there are instances where formulated co-crystals exhibit DSC peaks outside the range of the pure API and co-former, suggesting that this rule may not universally apply to confirm co-crystal formation.DSC is valued for its rapidity and efficiency in characterizing co-crystals, as it is a solvent-free method requiring only a small sample size for analysis [82]. For example, Enxian Lu and colleagues employed DSC to screen 16 co-crystals, including nine newly synthesized ones not previously reported in the literature. One notable co-crystal they prepared was of salicylic acid with caffeine, which exhibited a melting point lower than those of salicylic acid and caffeine individually, possibly due to the eutectic nature of their mixture [74]. Further research is needed to accumulate more data to aid in the selection of co-formers and to confirm co-crystal structures.Moreover, the measurement of heat energy can also be utilized to confirm the formation of co-crystals, as co-crystals typically exhibit reduced heat energy compared to the pure API used [82].

5.2.2. Hot stage microscopy (hsm):

HSM is popularly known for the characterization and screening of co-crystals. HSM allows users to observe recrystallization and crystal growth of melted components of co-crystal. Characterization and screening of co-crystals can be done by using Kofler mixed fusion method [83]. In this method at the interface of two

components, the crystalline material is observed and that suggests the possibility of co-crystal formation between co-crystal components. David J. Berry and co-workers have screened and characterized five API mixtures for the formation of co-crystals using the Kofler mixed fusion method by hot stage microscopy method [84]. Thermal methods of characterization and screening are rapid and convenient for co-crystals. The limiting factor of this method is that only thermally stable materials can be evaluated.

5.3. spectroscopy:

Spectroscopic characterization of co-crystals can be classified into two main types. The first is vibrational spectroscopy and the second is Nuclear magnetic resonance spectroscopy. The vibrational spectroscopic method is subdivided into FTIR spectroscopy and Raman spectroscopy. IR spectroscopy works on the absorption mechanism and Raman spectroscopy works on the scattering mechanism of spectroscopy. The NMR spectroscopy method is a very powerful tool to obtain detailed structural information about multicomponent systems.

5.3.1. Fourier transform infrared spectroscopy:

FTIR spectroscopy is a very efficient tool to identify the formation of co-crystals. The formation of co-crystals is confirmed by a change in vibrational energy peaks in spectra, mainly due to the formation of hydrogen bonding in the functional group of co-crystal components. FTIR spectra of pure co-crystal components and formulated co-crystals are compared for detection of co-crystal formation and structural elucidation [85]. D.C. Sakhiya and C.H. Borkhataria Heliyon 10 (2024) e29057 10 Harry G. Brittain analyzed cinchona alkaloid-5 nitro barbituric acid co-crystals using FTIR spectroscopy. The study observes variations in absorption spectra of co-crystal and co-crystal components [86].

5.3.2. Raman spectroscopy:

Raman spectroscopy is an in-situ monitoring and characterization method for co-crystal formation confirmation [87,88]. Raman spectroscopy exhibits better accuracy, precision, and sensitivity than the FTIR method. Raman spectroscopy can differentiate between co-crystal form and ionic form of multi-component systems. Evaluation of the formation of co-crystals is done by comparing the change in the oscillation of co-crystals in comparison to co-crystal components [76,87,89,90]. Yong Du and co-workers demonstrated potential applications of Raman spectroscopy in determining the co-crystal formation of nitrofurantoin and 4 aminobenzoic acid co-crystal components. Data obtained by Raman spectroscopy is useful for the discrimination of different multi-component pharmaceutical molecular solid systems [89]. K. C. Mullers at el. utilized color coding for fixed crystal patterns to identify raw ibuprofen and nicotinamide in the physical mixture and co-crystals and remaining coformer in the final product. Raman spectroscopic color-coded image of a final product shows the presence of formed co-crystals and some remaining coformer and no sign of the presence of pure ibuprofen [91].

5.3.3. Solid-state nmr spectroscopy:

SSNMR has the potential to provide detailed structural information about organic and pharmaceutical co-crystals. SSNMR provides higher information content and high-yield data as compared to vibrational spectroscopy and PXRD methods. SSNMR is a nondestructive method and requires a very small amount of samples for data collection. Frederica G. Vogt [77] and co-workers examined several molecular complexes and co-crystals to understand the capabilities of SSNMR. This study determines the ability of SSNMR to prove molecular association and observe structural features like hydrogen bonding [92,93]. Li Zhao and co-workers demonstrated the potential of dynamic nuclear polarization enhanced SSNMR method for the characterization of co-crystals and salt forms. The NMR spectroscopy also measured the 1H–15 N dipolar coupling constants and H–N bond lengths more accurately. These parameters provide an unambiguous assignment of nitrogen protonation states and definitive differentiation of multicomponent systems as co-crystals or salts. This method can also solve major confusion of confirmation of the final product as co-crystals or as salts [93].

6. CONCLUSION:

Co-crystals represent a promising avenue for enhancing the physicochemical properties of active pharmaceutical ingredients (APIs). A variety of methods exist for preparing co-crystals, ranging from small-

scale laboratory synthesis to large-scale industrial processes. This review provides an overview of different co-crystal formation techniques, selection criteria for co-formers, and methods for characterizing co-crystals, supported by relevant examples.

The pharmaceutical industry is increasingly interested in co-crystals due to their potential to improve drug properties. Additionally, the ability to patent co-crystals is crucial for pharmaceutical companies to protect their investments and generate revenue from innovative formulations.As research progresses and the benefits of co-crystals become more evident, it is anticipated that co-crystals will become a standard approach in pharmaceutical development, offering tailored solutions for optimizing drug performance and efficacy.

7. Opinion of author:

Co-crystals represent an innovative approach in pharmaceutical development aimed at enhancing the physicochemical properties of active pharmaceutical ingredients (APIs) without the use of organic solvents, thereby reducing environmental impact. However, advanced methods such as electron spray and supercritical fluid technology, while environmentally friendly in terms of solvent use, require substantial electrical energy and expensive equipment for co-crystal synthesis.

Improvements in traditional methods like solvent evaporation, by controlling temperature and pressure during evaporation, can enhance co-crystal formation without the need for high-end equipment. Despite their potential environmental benefits, methods like electron spray and supercritical fluid technology consume significant energy and necessitate skilled operators.

Confirming the synthesis of co-crystals remains a challenge, typically assessed using PXRD and single-crystal XRD, which can be costly. Differential scanning calorimetry offers an alternative for screening effective co-formers, though it struggles when API and co-former have similar melting points. There is a need for a more cost-effective method to confirm co-crystal synthesis.

Quantifying co-crystals in the final product is challenging with conventional methods. Raman spectroscopy shows promise in detecting unreacted materials, while NMR spectroscopy accurately determines bonds involved in co-crystallization, potentially replacing X-ray diffraction methods in the future due to its simplicity and interpretability.

Co-crystals are gaining popularity due to their superior properties such as compressibility, flowability, hygroscopicity, and improved drug stability compared to salts. Their patentability offers researchers and developers exclusive rights, fostering innovation in drug formulation and potentially revitalizing older drugs for improved healthcare solutions.

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