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Application Of Co-Crystallization Mixed Hydrotropy And Melt Sonocrystallization Techniques In Enhancement Of The Solubility Of Poorly Water Soluble Drugs

A CRITICAL REVIEW

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Abstract: The current review paper is based on the three distinct techniques used to increase the solubility of specific BCS class II drugs i.e. Melt sonocrystallization, co-crystallization and mixed hydrotrophy. One of the important pre-formulation characteristics that control the intended drug concentration in the systemic circulation is solubility. The majority of recently identified chemical entities exhibit low solubility, which subsequently results in low bioavailability. Co-crystallization is also used mainly for the enhancement of solubility of BCS class II drugs. The development of co-crystals can improve the solubility of poorly soluble drugs; various techniques for the preparation of co-crystals have been used hot-melt extrusion, spray drying, supercritical fluid technology and slurry method. Melt sonocrystallization is a recently developed particle engineering technique that produces fine drug particles that aid in improving aqueous solubility and bioavailability by using ultrasound energy. A technique known as "mixed hydrotropic solubilization" makes use of several hydrotropic substances to increase the solubility of medications that are not very water soluble.

Keywords: Solubility, BCS class II, co-crystallization, Mix hydrotrophy, Melt sonocrystallization.

1. INTRODUCTION

The low aqueous solubility of new chemical entities poses a significant challenge to the pharmaceutical industry's development. Based on their solubility and permeability, drugs are classified into four classes by the biopharmaceutical classification system (BCS). Class II drugs are characterized by high permeability and low solubility, as well as dissolution-limited absorption. It might be difficult to obtain the appropriate concentration of the intended pharmacological action due to the limited solubility [1].

Solubility is the concentration of a solute in a saturated solution at a given temperature. The type of solvent used, along with temperature and pressure, all influence a solvent's solubility. Solubility varies over time, from completely soluble (ethanol in water) to barely soluble (silver chloride in water). Insoluble compounds are those that are poorly or extremely insoluble. Solubility is an important condition for achieving target drug concentration in systemic circulation to demonstrate a pharmacological reaction. Hydrophobic drugs also enable large doses to achieve therapeutic plasma concentrations after oral administration [2]. In other words, a substance's solubility refers to its capacity to combine with another substance to form a solution. Delivery of some current medications is frequently hampered by solubility problems, which also prevent the delivery of these novel medications [3].

1.1 SIGNIFICANCE OF SOLUBILITY ENHANCEMENT

1. Solubility is one of the essential requirements for reaching the permitted drug concentration in systemic circulation to produce the required pharmacological reaction.
2. Hydrophobic pharmaceutical drugs often require high doses and a high dosage regimen to affect post-administration plasma concentrations.
3. Poor aqueous solubility is the primary concern in the development and manufacture of NCEs and generic drugs.
4. For drugs taken orally, solubility is one of the most crucial dose-limiting requirements in order to reach the desired concentration in full circulation for pharmacological response.
5. Water is an excellent solvent for liquid medicine formulations.
6. Most medications, such as those that are weakly basic or acidic, have a low aqueous or water solubility.
7. Inadequate and gastrointestinal toxicity of the mucosa, as well as variable bioavailability, are the result of poorly absorbed water-soluble drugs [4].
8. Solubility frequently indicates that parenteral formulation and other measurement mechanisms play a crucial role. One of the key pre-requisites for attaining the pharmacological response required to reach the ideal drug concentration in systemic circulation is solvency. Ineffectively, high doses of water solvent medications are frequently needed to achieve restorative plasma fixations following oral organization [5].

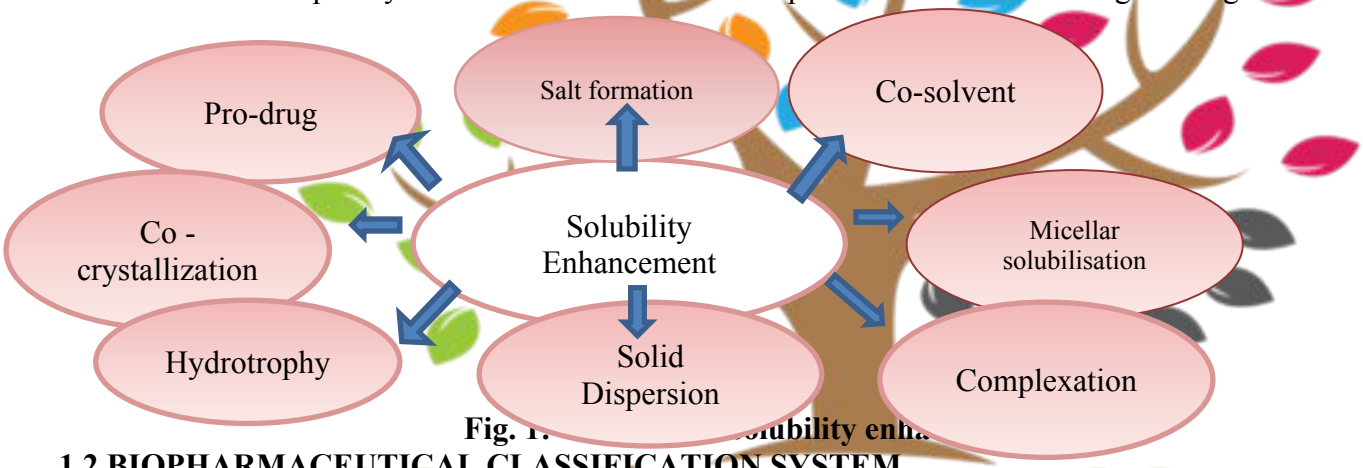


Fig. 1: Solubility enha

1.2 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

Table 1: BCS class with Examples of Drugs [7]

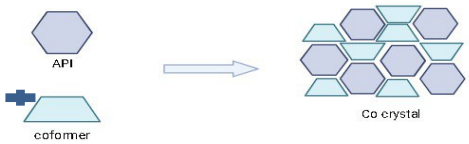
BCS	Solubility	Permeability	Examples
I	High	High	Diazepam,Acyclovir, Levodopa
II	Low	High	Nifedipine, Naproxen, Amlodipine, Itraconazole
III	High	Low	Nephazolin, Metformin
IV	Low	Low	Clorthiazol, Colistin,taxol

A scientific framework known as the BCS is used to classify drug substances according to their intestinal permeability and solubility in water. It is a tool for drug development that makes it possible to estimate the relative contributions of the three main factors - intestinal permeability, dissolution and solubility - that influence drug oral absorption. Drugs from BCS classes 2 and 4, drugs that have low solubility and provide a variety of tasks for formulation scientists working on drug delivery systems [6].

2. TECHNIQUES:

2.1 Co-crystallization

Co-crystallization is a method that is frequently employed by researchers to adjust the physicochemical characteristics of an active pharmaceutical ingredient (API) [8-10]. A co-crystal is a solid state material made up of several components held together at room temperature by Vander Waals forces, aromatic-aromatic interactions and hydrogen bonds, among other non-covalent bonds [11-12]. A pharmaceutical co-crystal is typically made up of two components: an API and an API with a suitable co-former. Pharmaceutical co-crystals are commonly formed using carboxylic acids and amides as co-formers [13]. API co-crystallization is the most commonly used technique for optimizing physiochemical properties while preserving molecular structure.



The physiochemical characteristics of solubility, dissolution rate, moisture uptake, stability and bioavailability are believed to be fixed by co-crystallization. The three most popular processes for creating co-crystals are melt crystallization, solution crystallization and mechanical grinding. On the other hand, additional techniques consist of melt-extrusion, sonic-slurring, rapid evaporation, super-critical fluids, anti-solvent addition, wet compression and dry compression [14].

Co-crystallization by evaporation of stoichiometric solutions is the general technique to co-crystal [13].

METHOD OF CO-CRYSTAL PREPARATION:

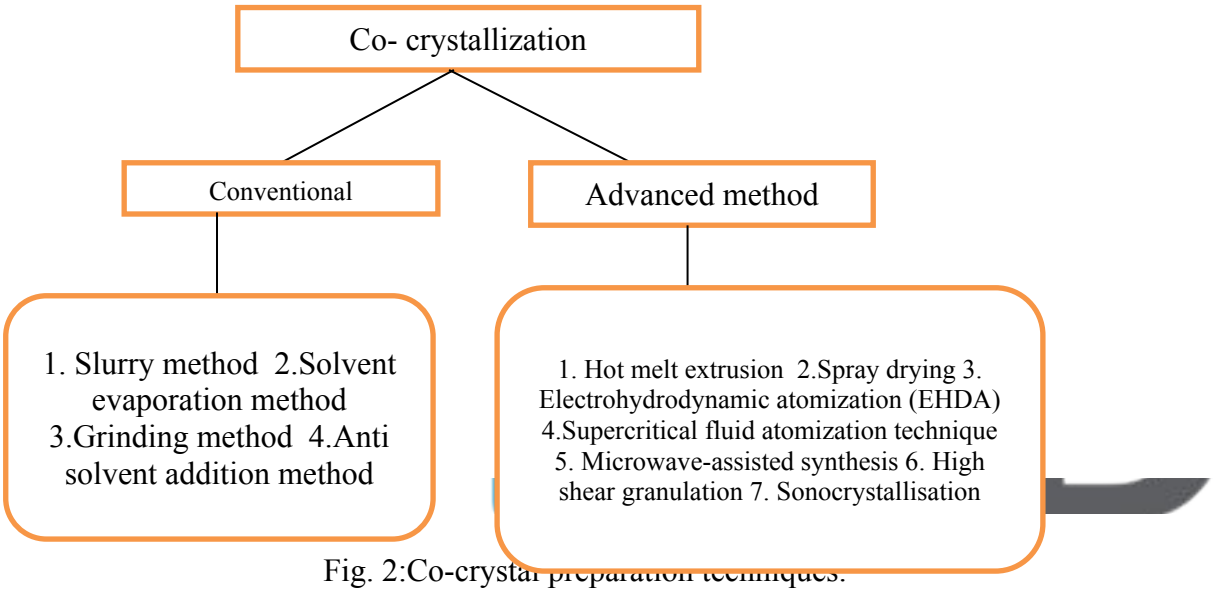


Fig. 2:Co-crystal preparation techniques.

CO- CRYSTALLIZATION TECHNIQUES

Cocrystals can be prepared primarily in two ways: solution-based and solid-state-based. Each approach has advantages and disadvantages. Solid-state methods are often used to prepare cocrystals in both the laboratory and industry. They are versatile, eco-friendly and sustainable. Solution-based methods, on the other hand, are simpler and easier to control, but they are mainly suitable for lab-scale preparations. It's important to choose solvents carefully when using this method, as the characteristics of the cocrystals can be affected by the solvent selection. [14]

2.2 Preparation for Solid-State Methods.

Contact Formation Method

The method of forming contacts involves reducing particle size through increased crystallization rates [15]. It has been shown that pre-milled crystals significantly contribute to the spontaneous reaction for the formation of cocrystals[16]. This method has been used to prepare many cocrystals, demonstrating that smaller particles lead to faster cocrystal formation. For example, when particle size is reduced and the surface energetics of urea and 2-methoxybenzamide increases [18].

2.3 Solid-State Grinding Method

Solid-state grinding has been a well-known technique in research to prepare cocrystals for several years. One way to use it is to produce diastereomeric cocrystals of malic and tartaric acids through liquid-assisted grinding (LAG) in the solid state [19]. This approach involves two different methods for creating molecular assemblies: There are two methods used for grinding: the neat or dry grinding (DG) method and the LAG method.

2.4 Dry or Neat Grinding Method

In the dry grinding method, the solid forms of the API and conformer are ground together mechanically in a ball mill or manually with a mortar and pestle.[20] One medication that is included in BCS Class II is brexpiprazole. The ball milling technique, a practical way to prepare cocrystals with conformers like succinic acid and catechol, is used to increase its solubility. [21] However, the dry grinding method has a significant disadvantage: it cannot guarantee the formation of a stoichiometry mixing of cocrystals, necessitating an additional step to obtain a pure cocrystal product.

2.5 Liquid-Assisted Grinding Method

Cocrystals are valued in the pharmaceutical industry for their enhanced solubility, bioavailability and stability.[22] The LAG (Liquid-Assisted Grinding) method is a popular technique for the preparation of cocrystals. This method involves the addition of a small amount of solvent to the mixture, which can act as a catalyst to accelerate the reaction kinetics and aid in the formation of cocrystals. Research has demonstrated that LAG is a quicker and more effective way to screen cocrystal hydrates than dry or neat grinding methods[23]. It has also been discovered to provide compatible results regardless of the nature of the reactant, making it a preferred method for pharmaceutical cocrystal screening.[24]

One notable example of the LAG method's successful application is the preparation of the cocrystal of piracetam, a nootropic drug, using both dry and LAG methods. The use of suitable solvents in the LAG method was found to accelerate the reaction kinetics and produce the desired cocrystal product. Furthermore, the formation of carbamazepine cocrystals with nicotinamide and saccharin demonstrates the ease of the solvent drop method for cocrystal preparation. [25]

Although LAG and DG (Dry Grinding) methods are low-cost, simple to use and environmentally friendly, they might not be appropriate for industries that require large-scale production. Hot melt extrusion (HME) is recommended in these circumstances.[26]

2.6 Hot-Melt Extrusion:

The HME method is a popular technique used in the pharmaceutical industry. Over the last decade, this method has proven to be effective in replacing old methods of preparing cocrystals and can be used in both laboratories and commercially [27]. In this method, both the API and conformer are mixed simultaneously with the help of heat and pressure, above their melting points. When first presented the HME method for creating cocrystals, they discovered that increased molecular surface contact and homogeneous mixing could greatly aid in the process [28]. The HME method requires careful consideration when choosing extruders. A twin-screw extruder could be used to guarantee an appropriate homogeneous mixture of components for pharmaceutical cocrystal preparation. An important consideration in the HME method is temperature.[29] Reported the formation of cocrystals with ibuprofen and nicotinamide. They found that increasing the temperature above the eutectic point enhances mixing, speeds up the rate of dissolution and gets rid of the size reduction step. The cocrystal quality is also impacted by screw configuration [30]. High screw rotational speed can degrade the product; low screw rotational speed is necessary to obtain high-quality cocrystals[31]. HME is useful in a variety of applications; for instance, it can function as a reaction vessel to generate cocrystals, which improve the bioavailability of APIs that are poorly soluble in water. Thus, HME is a dependable technique that can easily accommodate shifting regulatory requirements, is solvent-free and can be used in a single step to replace other antiquated techniques.

2.7 High Shear Wet Granulation:

Using a high-shear granulator, powder components are mixed in a liquid medium in the high-shear wet granulation (HSG) method. Cocrystal components can also be produced in large batches using this technique. The speed of the impeller, the type of excipient used and the length of time the granules are exposed are some of the variables that affect granule formation. [32]. Choosing the right liquid media for granulation is crucial to achieve the desired outcome.

Veronika et al. successfully produced cocrystals of ivabradine hydrochloride with the conformer S-mandelic acid using the wet granulation method. Additionally, the researchers looked into how excipients affected the stability of the cocrystals during the wet granulation process and discovered that they did not affect the creation of cocrystals of ivabradine–mandelic acid [33].

However, medications with complicated processes and thermal lability might not be suitable for the HSG method. Thus, an appropriate technique must be chosen based on the sample type and the required quality of cocrystal formation.

2.8 Solution-Based Preparation Method:
The solution-based approach is one of the several methods for making cocrystals. This process includes isothermal slurry conversion, cooling crystallization, reaction cocrystallization and evaporative cocrystallization. One useful tool for creating cocrystals from a solution is the cocrystal operating range. This range can be found by locating the eutectic points in a solution that contains a combination of cocrystals and conformers. The explanation provided by the ternary phase diagram explains this range as well as the cocrystal stability [34].

2.9 Evaporative Cocrystallization:
The active pharmaceutical ingredient (API) and conformer are two of the cocrystal components that are created using this method using a volatile solvent [35]. The components of the solution reach a supersaturated concentration when it is maintained at room temperature due to the solvent's gradual evaporation a result, crystals begin to form and grow. Pharmaceutical cocrystals can be produced with this method, which is especially helpful [36]. For example, ibuprofen-nicotinamide cocrystals were created using this method in ethanol solvent. This method's simplicity, high potency during screening, and ease of handling are its advantages. Nevertheless, there are certain drawbacks to the method, including the potential for solvate formation, the challenge of scaling up, and the overuse of organic solvents, which can have negative environmental effects [37].

2.10 Cooling Crystallization:
Temperature plays a critical role in the process of crystallization. Depending on the compound, an increase in temperature can cause an increase in solubility. On the other hand, for supersaturated solutions, cooling the mixture can lead to the formation of cocrystals as precipitates. The primary goal of this technique is to create cocrystals that are as uniform as possible with maximum efficiency[38]. This is carried out by heating the solution to release the latent heat and cooling it to release the residual heat. Pressure is used to periodically circulate and cool the heated solution during this process. Some instruments use an evaporative system as well. Caffeine and glutaric acid cocrystals are made in acetonitrile using this preparative technique. Among the techniques available under this method are vacuum cooling crystallizers, continuous cooling crystallizers and scraped surface cooling crystallizers.

2.11 Reaction Crystallization:
Cocrystals can be produced by mixing a solution holding reactants with another solution and stirring the resulting mixture in a vessel. This process causes the concentration to exceed the solubility limit, leading to the formation of crystals. Mixing conditions affect the crystal size and microstate mixing - which produces supersaturation and lowers solubility - determines the nucleation growth. These processes enable nucleation and crystal formation. For example, carbamazepine can form cocrystals with nicotinamide using this technique [40]. However, there are some drawbacks to this method, such as the use of hazardous solvents, the formation of solvates in the yield and difficulty in scaling up.

2.12 Isothermal Slurry Conversion :
The most effective technique for screening and increasing cocrystallization is a Isothermal Slurry Conversion method [41]. It entails stirring for a predetermined amount of time after dissolving the conformer and API in various solutions at the proper temperature. Subsequently, nucleation growth leading to crystal formation is enabled when the constituent concentration surpasses the critical activity of the conformer (42). Through isothermal slurry conversion, it was discovered that there was a stable form of theophylline-aspirin crystal in isopropyl alcohol(43).
Cocrystals can be prepared using this method with less equipment and with relative ease. Nevertheless, because hazardous solvents are used, it is not environmentally friendly, and the process of scaling up is difficult.

2.13 Supercritical Fluid Methods:
Using a certain technique, we can alter the morphology and reduce the size of particles in a single step, which is highly advantageous for cocrystallization and results in the highest quality crystals. For this method, CO_2 is the most often used supercritical fluid. It has several benefits, including fewer processing steps, being an environmentally friendly solvent, generating well-finished products without the need for

solvents, a higher propensity for solubility and less product degradation because of the lower temperatures (31°C, 7.39 MPa) [44,45,46].

2.14 Rapid Expansion of Supercritical Solution:
One of the methods for producing fine microparticle crystals is the rapid expansion of the supercritical solution. In supercritical fluid CO_2, this entails depressurizing the conformer and API solution at atmospheric pressure. In the supercritical CO_2, the solvent fluid gradually decreases to supersaturation, which causes nucleation growth and ultimately crystal formation. This technique increased letrozole's solubility by 7.1 times. However, this method's disadvantage is that it produces low yields because only specific pairs of conformer-drug combinations are soluble in CO_2 [46].

2.15 Supercritical Solvent Crystallization
The supercritical solvent crystallization technique utilizes carbon dioxide (CO_2) as a solvent, negating the need for additional organic solvents. This methodology relies on CO_2's capacity to induce intermolecular interactions that result in crystal formation via nucleation and growth. This technique boasts several advantages, such as the elimination of drying steps and the ability to control material solubility by adjusting CO_2's temperature and pressure conditions [47]. Researchers have achieved a high product yield by successfully obtaining crystals of indomethacin, saccharin, theophylline, and carbamazepine[48]. Since there is no water present, this method also has the advantage of not forming solvates or hydrates. Nevertheless, this method is only applicable to the creation of single-component crystals.

2.16 Supercritical Anti-Solvent Method:
Carbon dioxide (CO_2) is used as an antisolvent in the supercritical anti-solvent method due to its low solvent power toward the API and conformer. Ethanol and acetone are polar organic solvents that can dissolve the API and conformers. The solution containing the API and conformer is introduced into a high-pressure vessel filled with supercritical CO_2 fluid or sprayed into the precipitation chamber. When the fluid expands and the volume decreases, the solubility is reduced, resulting in the formation of supersaturated cocrystals (49).
For instance, the naproxen–nicotinamide microcrystalline ensemble was prepared using CO_2 as an antisolvent (50). This method is a single-step process, but it has some drawbacks, such as the use of hazardous solvents and the need for many special condition processes for the solvents.

2.17 Supercritical Assisted Spray Drying Method:
Atomization and supercritical fluid-enhanced atomization are two supercritical processes that operate in similar ways. Both methods involve depressurizing a solution containing cocrystal components and supercritical CO_2, which causes the liquid to split into fine droplets via a coaxial nozzle. In the atomization method, the droplets are sprayed into a drying chamber at atmospheric pressure, while in the other method, they are sprayed into chambers at the required pressures. CO_2 acts as an anti-solvent, and in the secondary stream, it can be replaced with N2 gas. To prepare itraconazole with L-malic acid crystals, tetrahydrofuran was flushed out and the final crystals were dried with more supercritical CO_2[52]. The anti-solvent crystallization method was also used to prepare pure theophylline crystals using different conformers via supercritical fluid-enhanced crystallization [53].

2.18 Miscellaneous Methods
Apart from the aforementioned popular methods, various methods are used to obtain the desired cocrystals.

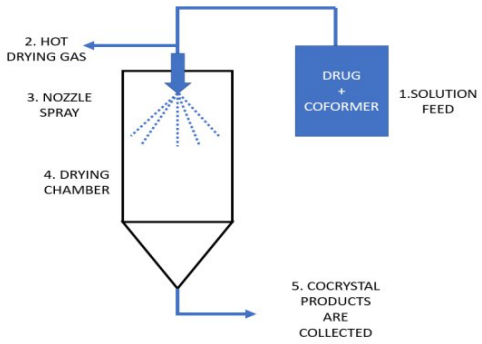
2.18.1 Laser Irradiation
The laser irradiation method is a novel way to prepare cocrystals. It uses a high-power CO_2 laser to vary the raster speed and power, stimulating the recrystallization of the conformer powder into a cocrystal framework. This method was used to prepare caffeine cocrystals containing oxalic acid and malonic acid[54].

2.18.2 Electrospray Technology
The electrospray technique is an exceptional and selective method for synthesizing cocrystals. This technique involves a single-step process that is highly efficient and precise when compared to traditional methods. The method uses an electric field to charge and elongate solution droplets, which causes the droplets to form elongated droplets. The lengthened solution droplets then undergo a process of desolvation, which leads to the formation of cocrystals. With this technique, researchers will be able to produce a large

variety of cocrystals with different properties, which will aid in the discovery of new drugs with improved solubility, bioavailability, and stability.[55]

2.18.3 Spray Drying Technique

Spray drying is a unique technique that can turn suspensions, emulsions or solutions into solid forms like agglomerates or powder. Although the pharmaceutical industry has long used this technique, it is now a vital tool for achieving high-quality standards in bulk density, moisture content and particle size and shape. Spray drying is a dependable means of producing cocrystals on a large scale and it is more practical than the Liquid Assisted Grinding method. Nonetheless, this method calls for costly and cumbersome equipment and has lower thermal efficiency. [56]



2.18.4 Freeze Drying:

By freezing and decreasing the ambient pressure, the freeze-drying method causes the material to sublimate, resulting in a phase change. Because it is used in large-scale production, freeze drying is a unique process with several advantages over other techniques, including the elimination of the problem of variations in the conformer solubility. According to the results of the cocrystal preparation of oxalic acid and theophylline [57], the freeze-drying method enables the formation of additional solid forms that are not possible with other conventional methods.

2.18.5 Electrochemically Induced Cocrystallization:

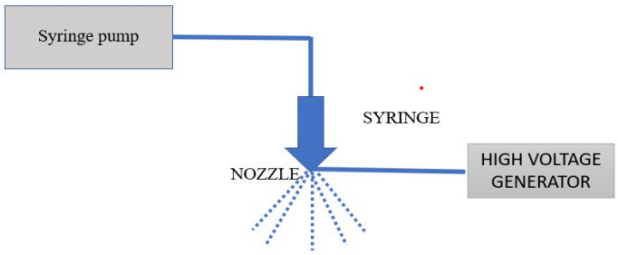
It is feasible to cocrystallize ionizable compounds through an electrochemically induced cocrystallization process. To prepare a cocrystal of 3-nitrobenzamide and cinnamic acid, the pH level can be shifted via electrochemical application to neutralize the carboxylic acids. This can serve as a catalyst for the cocrystallization process. (58)

2.18.6 Resonant Acoustic Mixing:

Resonant acoustic mixing is combining various ingredients with a suitable liquid to create the desired cocrystal without grinding them first. Several cocrystals of carbamazepine have been successfully formed using this method (59) by adding different solvents. Pre-blending and cocrystallizing the components allows this process to produce cocrystals on a large scale, which is one of its main advantages. Furthermore, the pharmaceutical industry can benefit enormously from the ability to re-slurry using the same equipment. Pre-blending and cocrystallizing the components allows this process to produce cocrystals on a large scale, which is one of its main advantages. Furthermore, the pharmaceutical industry can benefit enormously from the ability to re-slurry using the same equipment.

2.18.7 Electrohydrodynamic atomization (EHDA)

The EHDA technique is a process that involves the use of electrospinning technology to apply an electrically charged fluid. This method has good reproducibility and can operate continuously with ease by controlling the process parameters. In EHDA, a solution containing the dissolved drug material is discharged through an electric field. As a result, the solution droplets spread and eventually form a dried powder form through a capillary nozzle that is maintained at a high potential. The particles produced are then collected on a charged powder collector. This approach is mainly used for the production of nanocrystals, microcrystals, and cocrystals.[60].



2.18.8 Microwave-assisted synthesis:

In microwave-assisted synthesis, drug material and coformer are exposed to microwave radiation in a microwave reactor, either in the presence or absence of a solvent. The target time and temperature are determined using the drug and coformer microwave heating profiles that are kept constant throughout the experiment. Cocrystals eventually start to develop as a result of this. [61]

2.18.9 Ultrasound-assisted solution cocrystallization or sonocrystallisation:

Ultrasound-guided approach to separate substances, cocrystallization or sonocrystallization transforms an electrical signal into a physical vibration. These perturbations can dissolve dissolved gas from liquids, mix solutions and quicken the dissolution of a solid into a liquid. The air bubble contents quickly compress when supersaturation occurs. Because API and coformer were previously combined evenly, precipitation and crystallization are encouraged [62].

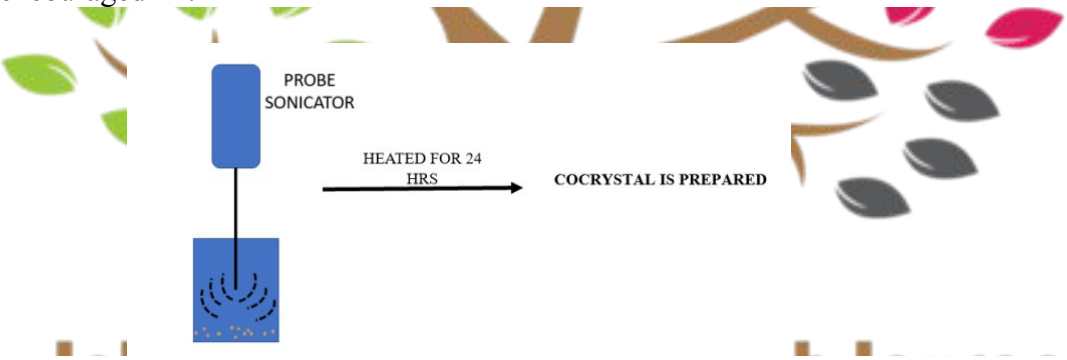


Table 2: Summarize report of Co-crystallization technique

Co-crystallization techniques	Drugs	Co-former	References
Solvent	Adefovir	succinic acid and +Suberic acid	63
	ketoconazole	Nicotinamide and 4-amino benzoic acid	64
	Ezetimibe	Benzoic acid and salicylic acid	65
	Mirtazapine	Oxalic acid	66
	Carbamazepine	nicotinamide	67
	Itraconazole	Malic acid and Tartaric acid	68
	Fluoxetine hydrochloride	Benzoic acid and fumaric acid	69
	Norfloxacin	Isonicotinamide	70
	Agomelatine	Urea and Glycolic acid	71
Solvent assisted grinding	Hydrochlorothiazide	Aerosil	72
Solvent exchange method	Aceclofenac	chitosan	73
Solvent drop grinding method	Diflunisal	Theophylline	74
Sonic slurry method	Carbamazepine	Saccharin nicotinamide	75
Liquid assisted grinding	Lomoxicam	Catechol, benzoic acid, and resorcinol	76

Solution crystallization	Febuxostat	Urea, nicotinamide,andacetamide,	77
Dry grinding	Paracetamol	Trimethylglycine	78
Solvent change method	Irbesartan	Chitosan	79
Slurry method	Quercetin	Isonicotinamide, Caffeine,	80
Solvent assisted grinding	Indomethacin	Saccharin	81
Liquid assisted grinding	Curcumin	Resorcinol	82
Solution, slurry and solvent drop grinding method	Meloxicam	Aspirin	83
Neat grinding, slow evaporation, and wet granulation	Niclosamide	Caffeine, urea, nicotinamide, isonicotinamide.	84
Supercritical fluid enhanced atomization technique	Theophylline, Indomethacin, Caffeine, Sulfamethazine.	Succinic acid	85
Spray drying technique	Efavirenz	Glutaric acid	86
Electrospray technology	Carbamazepine	Nicotinamide	87
Sublimation method	Urea	Succinic acid	88
Hot melt extrusion	Carbamazepine	Soluplus	89
Solvent evaporation	Glibenclamide	Tromethamine	90

Sr no.	Cocrystals [91,92]	Therapeutic Category
1.	Escitalopramoxalate-oxalic acid (Lexapro (R) Lundbek(R)	Treatment of depression
2.	Itraconazole	Antifungal
3.	Escitalopram oxalate	Depression and anxiety
4.	Valproate sodium cocrystal with valproic acid	Seizure disorder
5.	Entresto™	Chronic heart failure
6.	Suglat (Ipragliflozin cocrystal with L-Prolin)	Diabetes type II
7.	Beta chlor (Chloral hydrate cocrystal with betaine)	Insomnia
8.	Steglatro (Ertugliflozin cocrystal with Z-Pyroglutamic acid)	Diabetes type II

3. CHARACTERIZATION OF CO-CRYSTALS:

XRD Studies-single Crystalline and Powder XRD

Powder X-ray crystallography allows for the complete characterization of cocrystals. The drug's crystal lattice in the coformers can be detected through changes in diffraction patterns. Cocrystal structure and quantification are studied using powder XRD and single-crystal XRD, respectively. These methods can be used to characterize and quantify the percentage of cocrystal formation and determine the remaining components in the mixture during the manufacturing of cocrystals as an in-process assessment.[93,94]

3.1 Differential Scanning Calorimetry (DSC)

The pharmaceutical industry frequently uses differential scanning calorimetry (DSC) to assess cocrystals for a screening study, find contaminants, and ascertain the eutectic mixtur's formation. The pharmaceutical industry frequently uses differential scanning calorimetry (DSC) to assess cocrystals for a screening study, find contaminants, and ascertain the eutectic mixtures formation [95]. The melting point of the individual

compounds is different from that of the cocrystal when it forms. The thermogram shows the emergence of a new, sharp endothermic peak as a result[96].

3.2 Hot Stage Microscopy

In order to investigate the physical characteristics of solid materials as they vary with temperature and time, hot-stage microscopy is a technique that combines thermal analysis and microscopy. We can identify changes in the melting point, melting range, crystal development, crystalline transformations, and other thermal changes by using a microscope to watch the carefully regulated heating of drug crystals. This technique is especially helpful for examining the drug cocrystal crystal lattice [96].

3.3 Scanning Electron Microscopy (SEM)

A scanning electron microscope can be used to examine the surface morphology of cocrystals (SEM). The ZEISS Electron Microscope, EVO MA1 is the SEM used to investigate the surface characteristics of cocrystals[97]. This process involves sputtering the samples with gold in an argon atmosphere at room temperature, pelletizing them, and then mounting them to an aluminum stub with double-sided gold tape adhesive. To increase their conductivity, they are then put in a vacuum. After scanning the samples with an electronic beam, the resulting photos are examined to determine the surface characteristics [98].

3.4 Spectroscopic Studies

Two techniques can be used to study cocrystals: vibrational spectroscopy and nuclear magnetic resonance (NMR). Two types of vibrational spectroscopy are Raman and Fourier-transform infrared spectroscopy (FTIR). FTIR is used for predicting and evaluating chemical conformation, intermolecular interactions, elucidation of structure, and detection of cocrystal formation. Raman spectroscopy aids in the detection of polymorphic forms and is used to track the crystallization process. Cocrystals and polymorphic forms can be quantitatively analyzed using Fourier transform Raman spectra.NMR is a strong characterization method for organic pharmaceutical cocrystals and complexes, providing extensive information on their structure. Solid-state NMR can provide extensive structural information. SSNMR is a non-destructive approach for analyzing small volumes of powdered material that produces results with a higher information level than vibrational spectroscopy or powder XRD. Therefore, these spectroscopic analyses can be used to study the structural and quantitative analysis of cocrystals [96].

3.5 Mathematical Model of Solubility Studies

The process of cocrystallization is often used to increase an active pharmaceutical ingredient's (API) solubility. Nehm et al.'s mathematical model can be used to determine the solubility of the resultant cocrystal. This model states that the reaction in the solution reaches equilibrium when a 1:1 ratio of API (A) and coformer (B) is dissolved. It can be represented by the following equation,

$$AB \rightleftharpoons Asol + Bsol \quad (1)$$

$$Asol \rightleftharpoons Bsol + ABsol \quad (2)$$

Therefore, the equilibrium equation can be used to calculate Ksp (Solubility Product) and K11 (Complexation Constant in Solution Phase), where,

$$Ksp\ A = [A][B]$$

And

$$K11 = \frac{[AB]}{[A][B]\ Ksp} = AB$$

The following mass balance equations describe the total solubility of both drug and conformer and can be described as follows

$$[AT] = [A] + [AB]$$

And

$$[BT] = [B] + [AB]$$

Therefore,

$$[AT] = Ksp + \frac{Ksp.K11}{[B]}$$

The equation above shows that as the concentration of conformer increases, the solubility of cocrystal decreases. This means that the solubility of the conformer greatly affects the cocrystallization process.

3.6 Mixed Hydrotropy :

Neuberg coined the term "hydrotropy" which refers to the phenomenon wherein a solute becomes more soluble when alkali metal salts of different organic acids are added in relatively high concentrations[101,102]. Nonetheless, the term has been applied in the literature to describe substances that do not form micelles and can dissolve insoluble compounds. These substances can be liquids, solids, organic, or inorganic. Rather than being governed by a particular complexation event or a medium effect such as salting-in or co-solvency, the hydrotropic solubilization process suggests collective intermolecular interaction with multiple counteracting molecular forces. It is well known that adding hydrotropic agents can improve the poorly water-soluble drug's aqueous solubility. [103].

The process of "mixed hydrotropic solubilization" involves adding blends of hydrotropic agents to medications that have poor solubility in water to enhance their solubility. This method may have a synergistic effect on improving the solubility of medications that are not very soluble in water. Hydrotropic agents can be used to formulate dosage forms for drugs that are insoluble in water. Lowering the concentration of any one hydrotropic agent can potentially reduce any negative effects.[104,105].

Maheshwari examined the use of sodium citrate and urea combined to increase the solubility of aceclofenac, a medication that is poorly soluble in water. In order to dissolve the poorly water-soluble medication aceclofenac, which was taken as a fine powder from tablets for spectrophotometric analysis, a combination of hydrotropic agents was utilized, negating the need for organic solvents. A combination of hydrotropic agents was observed to have a remarkable synergistic effect.[106].

Advantages [107]

- Using a mixture of hydrotropic agents at lower concentrations can reduce the total concentration required to improve solubility.
- It is a novel technique for reducing the use of various organic solvents in the quantitative analysis of poorly water-soluble drugs. It is also simple, less expensive, safe, accurate, and eco-friendly.

Disadvantages of Hydrotrophy and Mixed Hydrotrophy [108]

- Water is used as a solvent in the hydrotropic agent, which makes it possible for weak interactions between the drug and the solvent to occur.
- There are certain limitations on the use of hydrotropes due to the toxicity of some hydrotropic agents.

3.8 Sonocrystallization

The application of ultrasound to regulate and expedite the crystallization process is known as sonocrystallization. Initially, the procedure involves more rapid nucleation that is relatively consistent across material volumes. This is a fairly straight forward nucleation technique for materials that are usually challenging to nucleate. Third, this produces the smaller and purer crystals, which are more uniform in size. The technique's yield makes it a more appealing size-reduction method than grinding [109,110]

The sonocrystallization process involves:

- Improved mass transport results in improved templating and clustering.
- After cavitation collapse, the temperature drops rapidly.
- A temporary high level of supersaturation occurs near a collapsing bubble.
- When pressure is increased, the temperature for crystallization decreases.
- Shock waves can be used to help initiate the process of nucleation.
- Breaking Through Energy Obstacles in Nucleation.[111]

3.9 Melt Sonocrystallization :

A novel technique in particle engineering called "melt sonocryatallization" applies ultrasonic (US) energy to a soft or viscous molten mass that is dispersed in an immiscible liquid. US energy handles the crystallization/solidification process from the emulsified melt. [113,112]. the method was first applied to the creation of sintered crystals and a porous glassy bead. The use of ultrasound allows the molten substance to absorb more energy from the US, while it is being mixed and controls the properties of the resulting particles. The rate at which the molten material solidifies and the ultrasound energy's frequency and intensity overshadow the features of the particles. This final variable, in turn, is dependent upon the medium's and the material's glass transition temperatures. An amorphous state is produced when the US is applied at temperatures below the transition temperature, whereas crystallization is favored when used at temperatures above it. In the case of ultra-sonication, the mechanical stress produces porous beads or sintered crystals. Improved solubility of poorly soluble pharmaceuticals is thought to be possible due toits porous nature and ability to produce both crystalline and amorphous particles, providing flexibility to the technology[114,115].

One method for producing drug particles with improved water solubility that does not require a solvent or carrier is melt crystallization. The method has been reported to enhance pharmaceutical solubility, micromeritics, and rheological properties.[116].

Process of Melt sonocrystallization [117].

The following is the generalized melt sonocrystallization procedure or method.

1. The required amount of medication was liquefied in a vessel on a paraffin oil bath maintained at a temperature between 190°C and 193°C.
2. The drug was then molten and put into a vessel filled with deionized water that was kept between 50 and 60°C.
3. Using a probe ultrasonicator with varying amplitude, the mixture was sonicated for 15 to 20 minutes.
4 After the droplets were distributed, the developed product was filtered and allowed to dry at room temperature.

CONCLUSION

Three different techniques—co-crystallization, mixed hydrotrophy, and melt sonocrystallization - were covered in this review. Several preparation techniques, including solvent evaporation, slurry methods, and crystallization from solution, were employed in co-crystallization, emphasizing the importance of choosing suitable co-formers and improving process conditions to produce the intended results.selecting the right co-formers is important because it has a great impact on how well co-crystallization works in improving drug solubility. A technique that shows potential for improving the solubility of BCS Class 2 medications is co-crystallization. Mixed hydrotrophy, which involves the combined use of multiple hydrotropic agents, has the potential to significantly enhance the solubility of BCS Class 2 drugs. This is crucial for improving the bioavailability of these drugs, as their low solubility often limits their absorption and efficacy. providing a pathway to overcome formulation challenges and improve the overall performance of these pharmaceutical compounds. Melt sonocrystallization can contribute to improved solubility of BCS Class 2 drugs by generating smaller and more uniform crystalline particles. This increased surface area facilitates faster dissolution and enhanced bioavailability.

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