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Review Article

Pharmaceutical Co-crystals: A Concise Review on Traditional and Novel Techniques for Preparation, Their Physiochemical Properties and Applications

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ABSTRACT

Cocrystals as defined by the FDA are, "Solids that are crystalline materials composed of two or more molecules in the same crystal lattice". Co-crystallization is a new approach of enhancement of solubility, stability, bioavailability and other physicochemical properties. Cocrystal can be made via the solvent evaporation method, grinding method, slurry process, cooling co-crystallization and anti-solvent method although each of these techniques has limitations under specific circumstances. The most novel techniques for creating crystals these are spray drying, supercritical fluid technology, microwave assisted, ultrasound assisted solution and, most recently, laser irradiation.

INTRODUCTION

The word "pharmaceutical co-crystal" refers to a single crystalline solid which includes two neutral molecules: an active pharmaceutical ingredient (API) and a co-crystal former, which is a solid at room temperature [1]. Co-crystals can improve other crucial characteristics such hygroscopicity, compressibility, powder flowability, and chemical and physical stability. They can also be helpful in the creation of novel co-crystal forms [2]. The process of forming co-crystals with an excipient, a different drug molecule, or a dissolving agent from an active pharmaceutical ingredient (API) might offer a way to build drug delivery systems at the molecular level and enhance some of the API's pharmacological qualities [3].

Pharmaceutical co-crystal further compounds, which consist of an API and a co-former and are often bound together by dependable hydrogen linked supramolecular synthons without the need for proton transfer, have also received attention subsequently [4]. The physicochemical properties of active pharmaceutical ingredients (APIs) such as melting point, aqueous solubility, dissolution rate, physicochemical stability, tablet compression production capacity, and bioavaialability can be enhanced through a novel method called co-crystallization of APIs and pharmaceutically acceptable co-formers, also known as generally acknowledged as safe (GRAS) materials [5]. Today, one of the main concerns of solid-state and materials chemistry is the study of crystal forms, such as solvates, salts, cocrystals, and their corresponding polymorphs, along with amorphous solid forms [6].

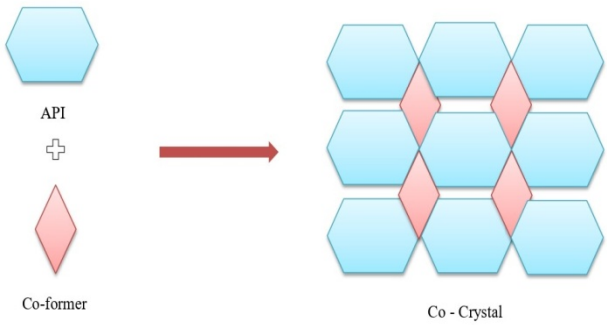

Figure 1: Schematic of co-crystal formation

One method that shows interest for increasing medication dissolving rate is co-crystallization. With this method, pharmaceuticals are formed into co-crystals with inactive co-formers. When as opposed to the original molecule, the new crystalline structures produced by this process

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dissolve more quickly [7]. Cocrystals can raise solubility above the drug's solubility by orders of magnitude in comparison with polymorphs. This is also the case with amorphous medicinal forms [8]. Finding good coformers continues to be one of the most important, if not the most important, factors in the success of co-crystal development [9]. Co-crystals give the possibility to customise a medication preparation's physicochemical characteristics to an ideal specification since they can possess characteristics that set them apart from the solid forms of the free API and its salts [10]. To increase kinetic solubility, co-crystallization and micronization are often used techniques [11].

An effective method for improving the water solubility and bioavailability of active pharmaceutical ingredients (an API) is co-crystallization [12]. Pharmaceutical co-crystals have mostly been made via solid-state grinding (neat and wet) and solution approaches (evaporation and cooling) [13]. Pharmaceutical co-crystals have advanced over the past decade in comparison to pure drug forms in a number of physical qualities, including solubility, bioavailability, and thermal stability [14].

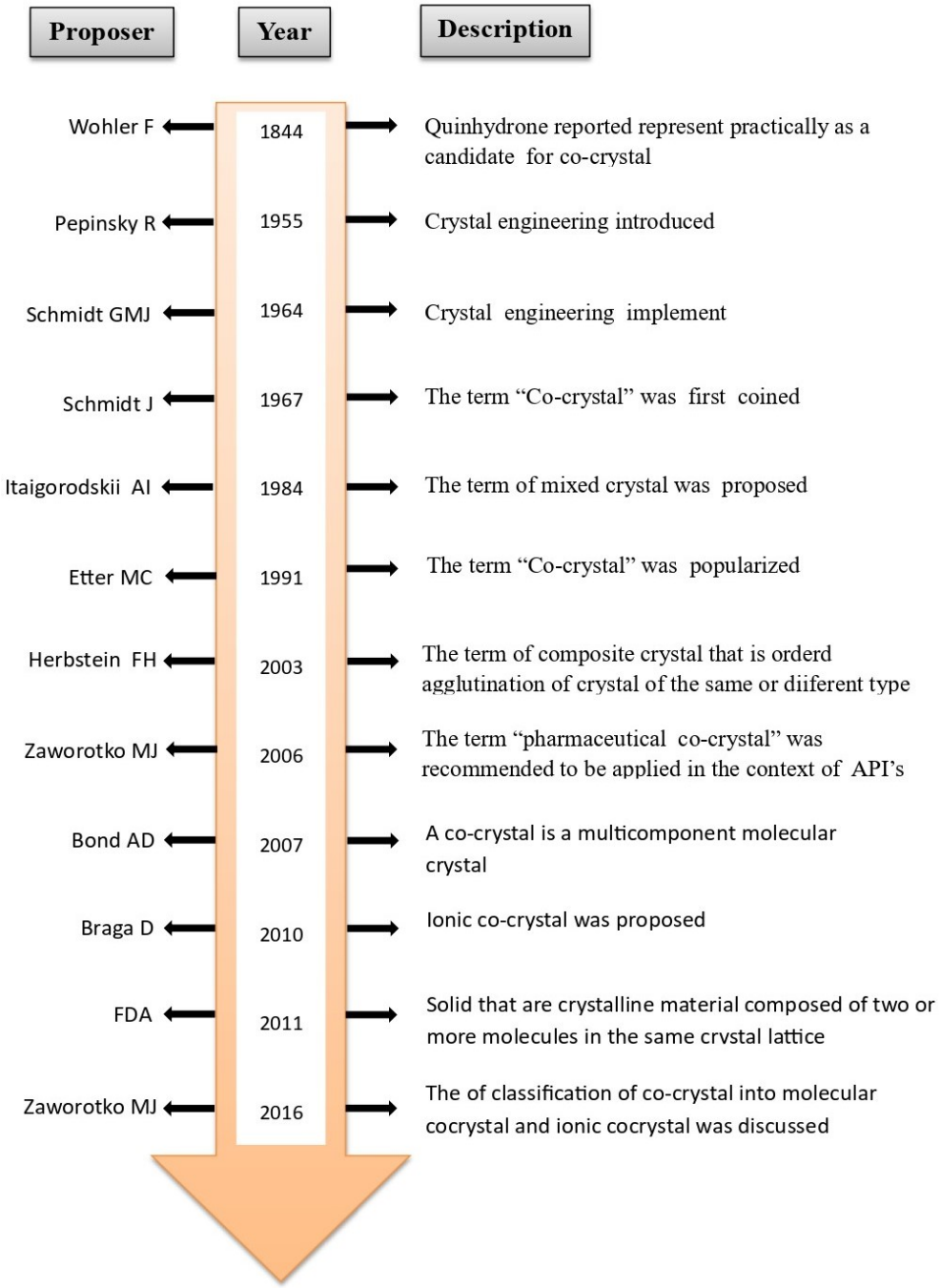

Figure 2: Historic diagram of co-crystal and its relatives [18]

Pharmaceutical cocrystal is an emerging technique that allows medicinal compounds to be modified in terms of solubility, rate of dissolution, and physical and chemical stability without affecting the drug's pharmacological impact [15].

It is the process by which two or more molecules with a certain stoichiometry produce a homogeneous crystalline substance in a single crystal lattice [16]. Disproportionation of cocrystals, or the precipitation of an original API that is poorly soluble, during dissolution must be avoided in order to reap the possible biological benefits of highly soluble cocrystals [17].

Methods of Cocrystallization

A. Traditional methods
B. Novel methods

A. Traditional Methods

1. Solvent Evaporation

One use for solution-based cocrystallization is the solvent evaporation technique for cocrystallization. This process involves dissolving the cocrystal components in a suitable solvent in appropriate stoichiometric ratios, and then letting the solvent evaporate entirely [19]. The polymer dissociates in appropriate water during the solvent evaporation procedure. The medication is dispersed in this polymeric solution, which is an immiscible solvent. To create discrete droplets, the resulting solution or dispersion is further emulsified in an aqueous continuous phase [20]. At all times during evaporation, the thermodynamic stability of molecules should be taken into account for the best possible outcome. The evaporation process's primary flaw is that it doesn't work well for large-scale preparations [21].

2. Slurry Method

A combination of solid particles suspended in a liquid is called as slurry. Slurries are employed in a variety of fields, including cocrystal transportation; in addition to the bulk movement of materials like dirt [22]. An alternative to creating cocrystal is to employ the slurry technique of processing.

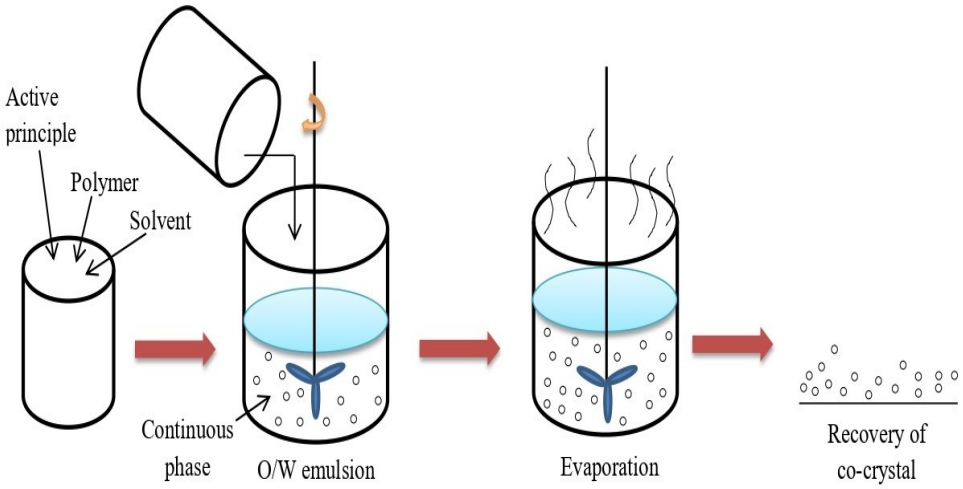

Figure 3: Solvent Evaporation Technique

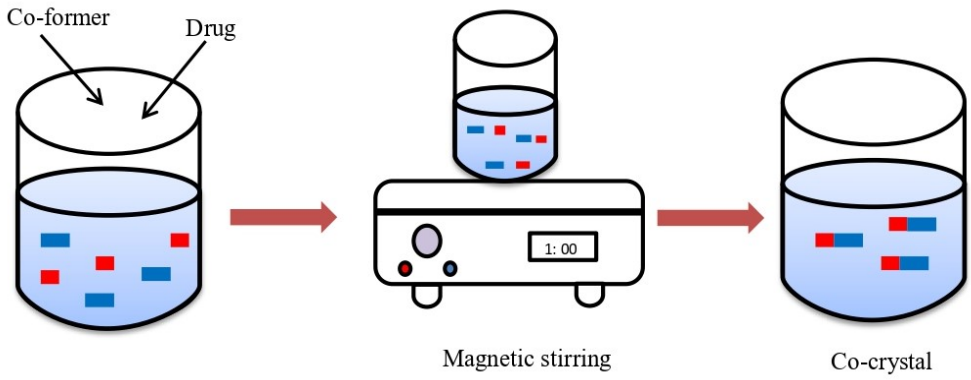

Figure 4: Slurry Conversion Technique

Using this procedure, the physical combination of API and conformer is mixed with a tiny quantity of solvent, and the mixture is stirred until the end outcome is cocrystal. A combination of drug and conformer is mixed with the solvent to facilitate the conversion of solid reactants into cocrystals [23].

To ascertain the most stable form and the correlation between thermodynamic stability among polymorphs, the slurry approach has been utilised [24]. Thus techniques have been approached to modify drug solubility with positive results, including nanoparticle, solid dispersion, and cocrystal [25].

3. Cooling Crystallization

An additional solution technique for co-crystal formation is cooling crystallisation. The process of chilling the co-crystalline solution results in the supersaturation needed for co-crystal development. Both co-formers become less soluble at a reduction in temperature, which increases the likelihood of precipitation and co-crystal development. Co-crystals of carbamazepine or nicotinamide derived from ethanol are among the co-crystals generated via cooling crystallisation [26].

4. Grinding Methods

This grinding method has gained popularity for two reasons: first, it uses not much or any solvent and its become environmentally friendly, and second, since this may be used as a screening tool to produce new co-crystalline phases that aren't thought to be present in typical crystallisation from solution [27].

a. Liquid assisted grinding
b. Dry or neat grinding

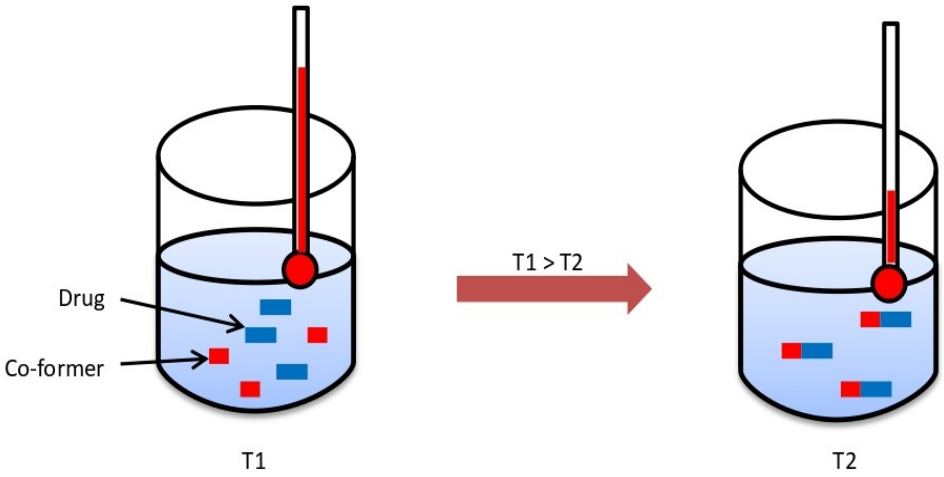

Figure 5: Cooling Co-Crystallisation

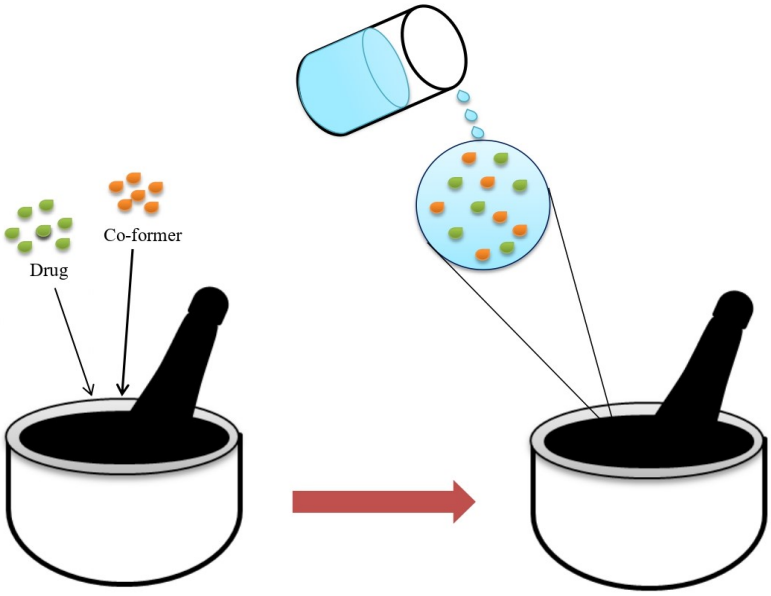

Figure 6: Liquid Assisted Grinding Method

a. Liquid Assisted Grinding

The method was originally termed solvent-drop grinding [28]. Liquid-assisted grinding, one of the mechano-chemical methods, effectively reduces the reaction energy barrier and accelerates the reaction [29]. In the event of liquid-assisted grinding, a liquid phase of water can be added to the process [30]. By addition of an appropriate solvent which acts as a lubricant for the reaction to facilitate molecular diffusion [31].

b. Solid State Or Neat Grinding

The process of combining, pressing, and crushing materials by hand using a mortar and pestle or mechanically in a mill is known as solid-state grinding [32]. The act of solid-state grinding to induce chemical change is known as mechanochemistry [33]. The typical grinding time is between thirty and sixty minutes. Numerous cocrystals may be created with this procedure, and any failure is usually the result of using the incorrect parameters [34].

5. Anti-Solvent Method

The vapour diffusion method, which is another name for the anti-solvent method, is a technique used to produce high-quality cocrystals [35]. An organic solvent-water combination is the solvent-antisolvent combination that is frequently utilised. For cocrystals with lesser solubility, antisolvent cocrystallization is a good substitute for evaporative and cooling cocrystallization [36].

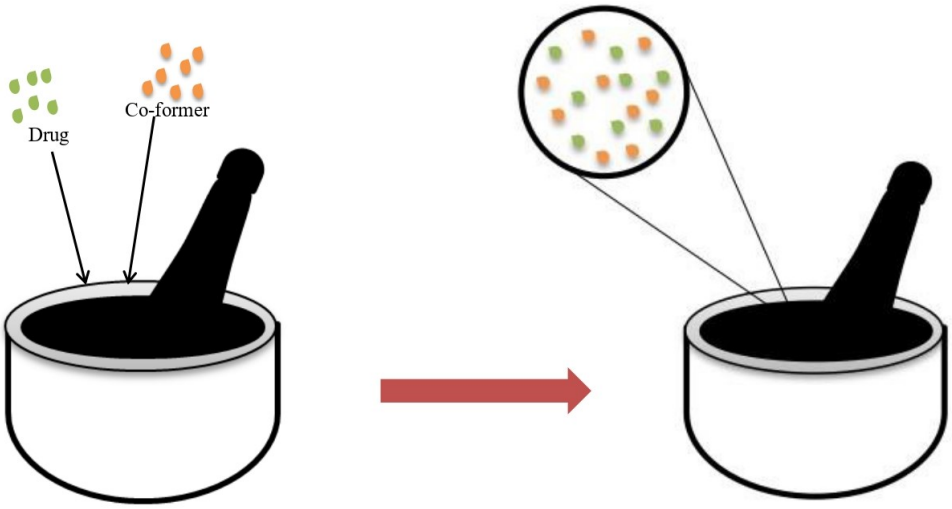

Figure 7: Solid State Grinding

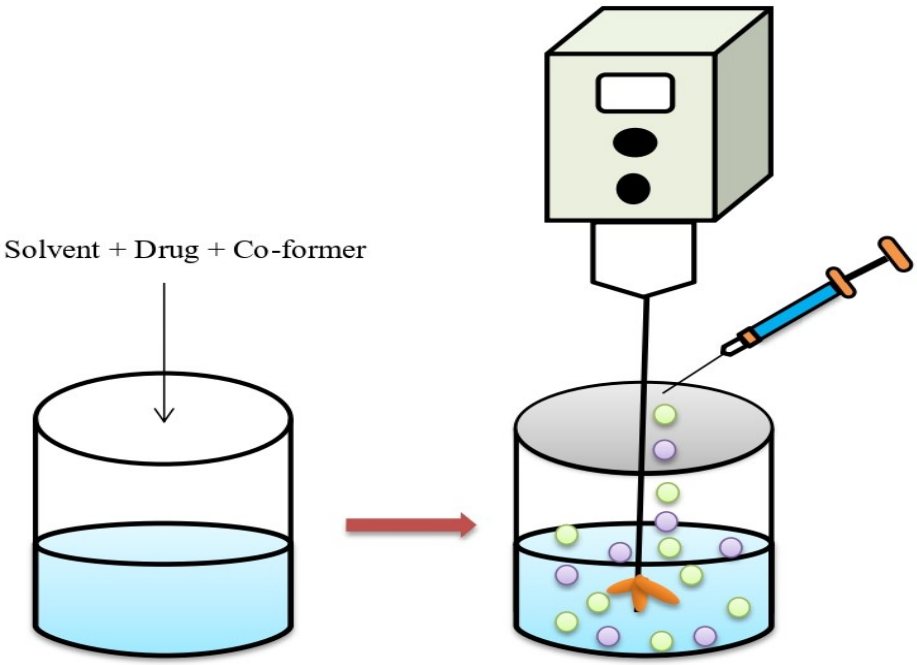

Figure 8: Anti-Solvent Method

B. Novel Methods

1. Supercritical Fluid Technology (SCFT)

In several areas of pharmaceutical applications, supercritical fluid technology (SCFT), a novel technique for producing tiny drug particles, is beneficial for batch uniformity, product quality, and lowering manufacturing challenges [37]. Gas antisolvent (GAS) is the primary supercritical fluid technology utilised in cocrystallization, Cocrystallization with Supercritical Solvent (CSS), Super-critical Antisolvent (SAS) and Enhancing Atomization with Supercritical Fluid (SEA) [38]. Since SCF technology is non-toxic, inert, affordable, and ecologically benign, it has attracted a lot of interest in the past few years [39].

2. Spray Drying

First discovered in 1860, spray drying is the method of turning an emulsion, solution, or suspension into dried powder in a single step by passing an atomized spray through a high-temperature gaseous medium [40, 41]. When a liquid is ground into a spray of tiny drops and placed in a drying chamber with heated air, the solvent quickly evaporates. This process is known as spray drying. The procedure is divided into four stages: spray-air interaction, evaporation of sprayed droplets, collecting product, and atomization that results in a solid into a spray nozzle [42].

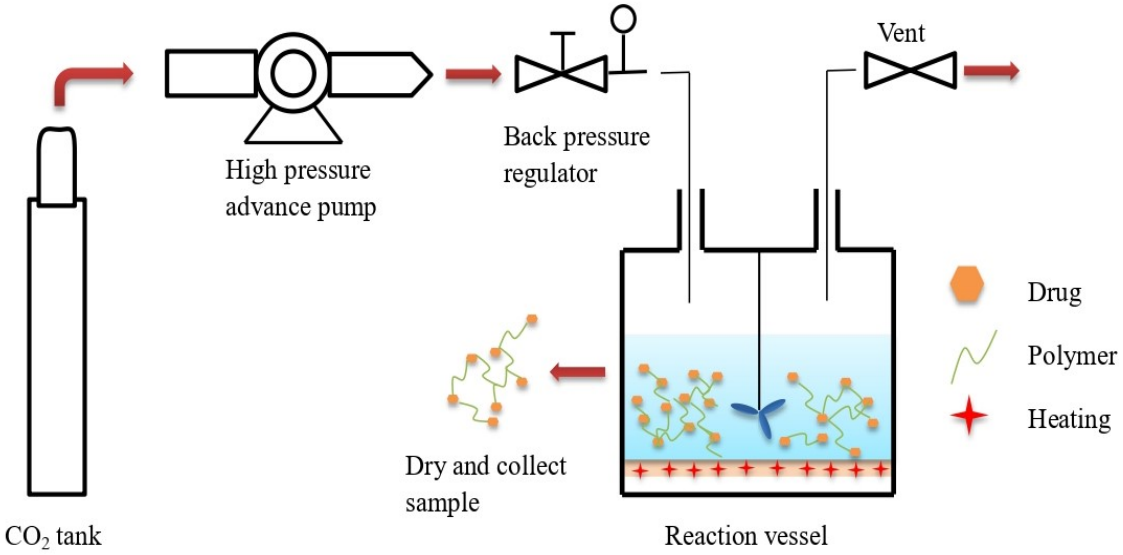

Figure 9: Supercritical Fluid Technology

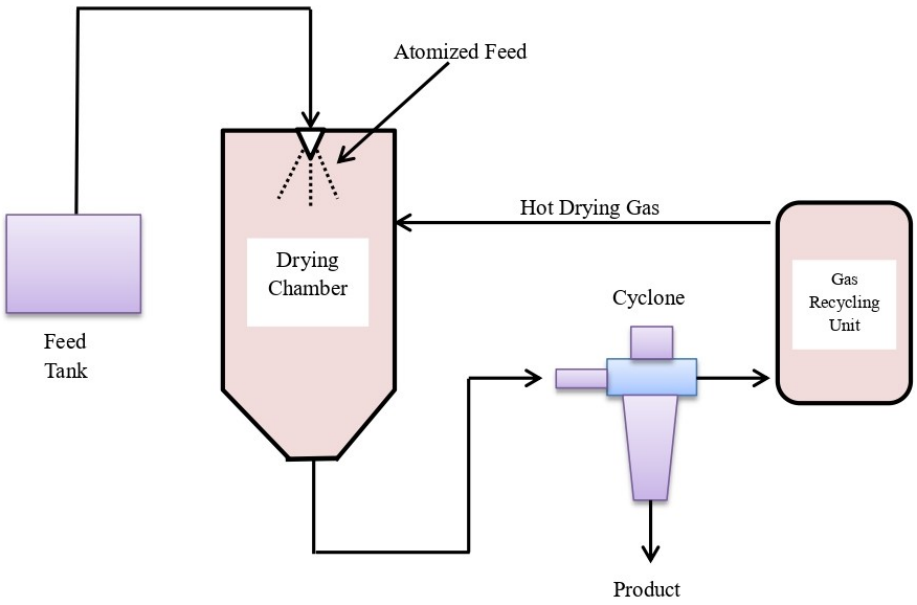

Figure 10: Spray Drying

Before spray drying, the excipient solution or suspension was combined with the cocrystal solution [43]. Pharmaceutical cocrystals of theophylline with urea, saccharin, and nicotinamide were engineered via spray drying for use in pulmonary applications [44].

3. Ultrasound Assisted Solution

In ultrasound-assisted resolution method, drug and coformer were dissolved together in solvent [45]. The solution is kept at a steady temperature in a sonicator to prevent fragmentation and degradation.

To allow the solvent to evaporate and the formation of cocrystals, the solution is left overnight [46]. Ultrasonic technology operating at 40°C and 42 kHz vibrations may provide up to 100 W of power [47]. The cavitation energy of ultrasonic waves during the application of ultrasound to a solution affects the nucleation from particle-free solution [48].

4. Microwave assisted co-crystallization

Drug substance (API) and coformer are used in equimolar levels in microwave aided synthesis and these equimolar ratios with or without solvent are exposed to microwave irradiation in a microwave reactor [49]. When electromagnetic waves in the frequency range of 0.3 to 300 GHz interact with polar and polarizable materials, they cause dielectric heating [50]. By interacting with the molecule's spinning dipoles, microwave radiations excite molecules and improve their mobility, which accelerates co-crystallization since the radiation heat keeps the supersaturated solvent from evaporating quickly [51].

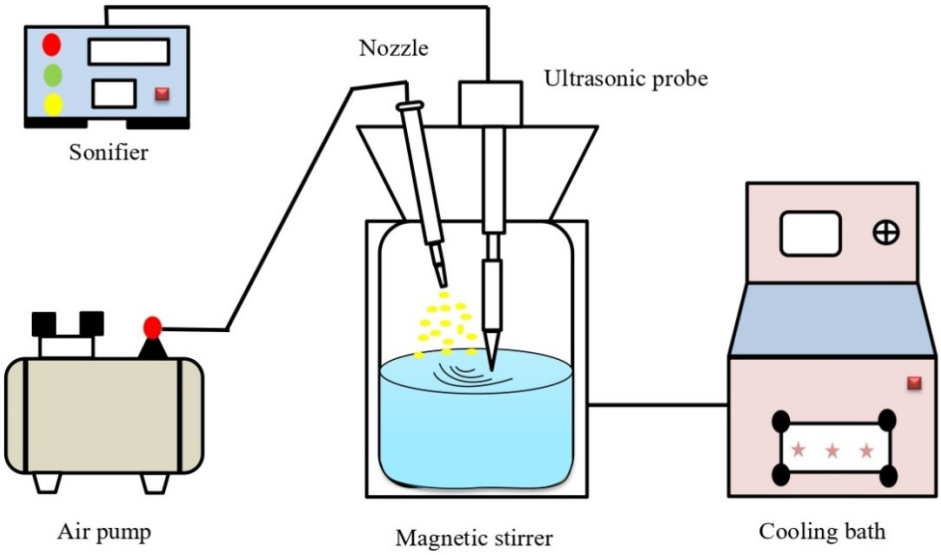

Figure 11: Ultrasonic Assisted Solution

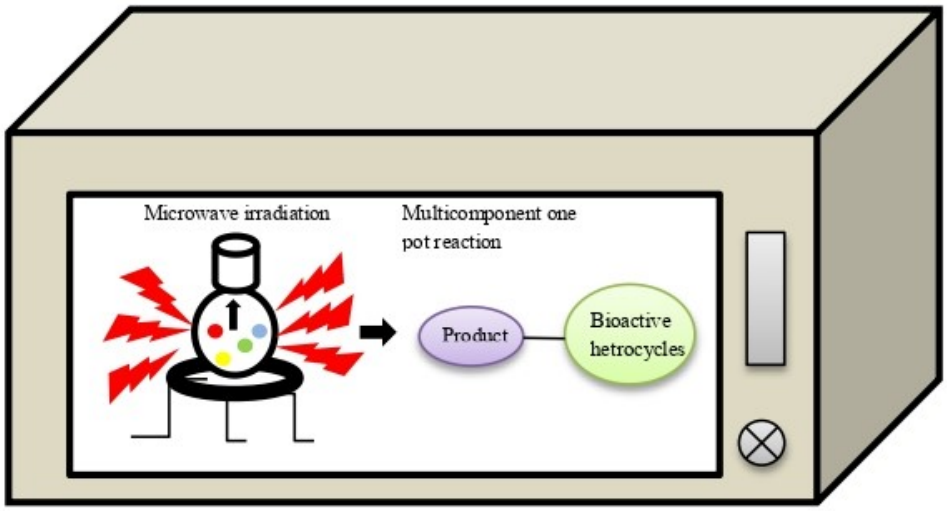

Figure 12: Microwave Assisted Co-Crystallisation

5. High Pressure Homogenization

This process uses mechanical energy for the fragmentation of suspended particles in a solvent system at high pressure. During the process of homogenization, the suspension generates turbulence due to high velocity, and that results in cavitation and thereby cocrystal formation [52-54]. This method has used to create nano-cocrystals of BE (Baicalein) Nano crystals and BE-NCT (Baicalein nicotinamide) using poloxamer 188 as a stabilizer [55].

6. Laser Irridiation

In this technique Co-crystal former powder mixtures were exposed to radiation using a high-power CO_2 laser. Hence, laser irradiation presents a fresh approach to the synthesis of medicinal co-crystals as well as a quick way to screen for conforming pairings that are likely to form co-crystals [56]. The energy that the sample received from the radiation caused a quick rise in temperature, which melted the crystalline substance and caused it to recrystallize quickly after cooling. To enable a nucleation process through vapour phase, one suggested need for coformer material that may be employed for this approach is sublimableness [57].

Physiochemical Properties of Co-Crystal

Melting Point

A fundamental physical attribute is the melting point, and the balance between the solid and liquid phases is indicated by the melting temperature. Since the co-crystal has a lower melting point than the API, we often choose it.

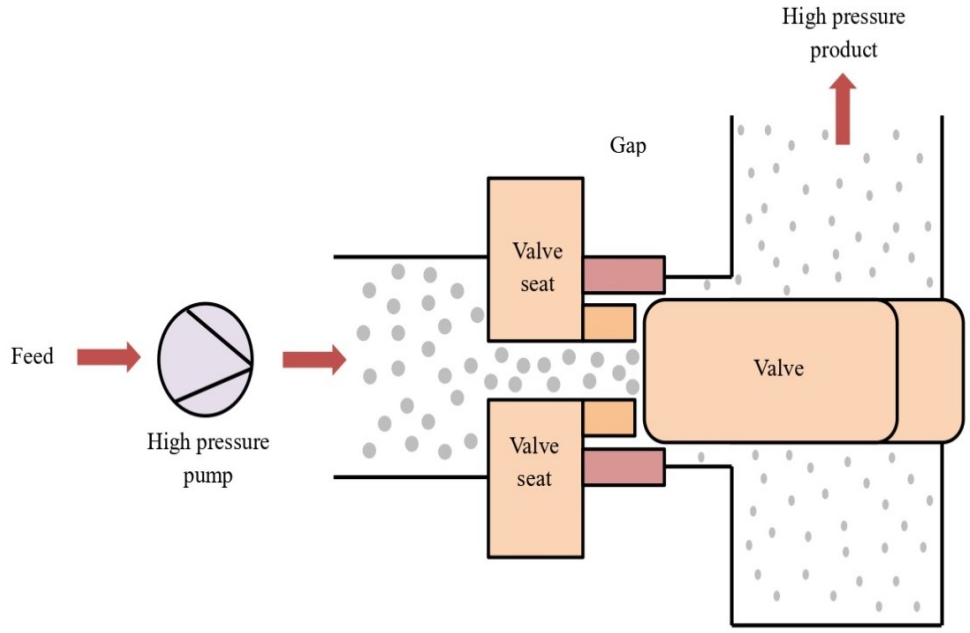

Figure 13: High Pressure Homogenisation

Table 1: Application and methods of pharmaceutical co-crystal

Sr. No	Drug	Co-former	Method	Pharmaceutical application	Ref
1.	5-Flurouracil	Gentisic acid	Solvent assisted grinding	Increased bioavailabilty	[58]
2.	Carvedilol	Hydrochlorothiazide	Slurry conversion and solvent evaporation	Enhanced solubility and permeability	[59]
3.	Glimepride	Succinic acid, theobromine and 1caffiene	Solvent drop grinding	Increased aqueous solubility	[60]
4.	Zaltaprofen	Nicotinamide and hydroquinone	Dry grinding	Increased solubility and dissolution rate	[61]
5.	Resveratrol	4-aminobenzamide and isoniazid	Liquid assisted grinding	Enhanced tabletability	[62]
6.	Telaprevir	4-aminosalicylic acid	Solevnt evaporation method	Enhanced oral absorption	[63]

For example, when trying to classify a polymorphic pair of chemicals as monotropic or enantiotropic, the melting point and heat of fusion, both found using DSC, are required [64].

Solubility

Greater solubility and subsequent absorption of the API may be made possible by the cocrystal form; as a result, less API may be needed in the dose form [65]. Since solubility influences a drug's absorption and bioavailability, improving solubility is a crucial topic in pharmaceutical research [66-69]. The pH of the solution mostly determines the co-crystal solubility of ionised drugs. This may be estimated by calculations based on the cocrystals degree of ionisation and dissociation constants [70].

Bioavailability

The amount that a medicine enters the systemic circulation is measured by its bioavailability. Research on dogs was conducted to determine how bioavailability enhanced glutaric acid and Cocrystals of 2-[4-(4-chloro-2 fluorphenoxy) phenyl] pyrimidine-4-carboxamide (PPPA). When the API was prepared in cocrystal form, it was found that the AUC increased thrice [71-74].

Stability

One crucial factor in the dosage form design process is stability. Cocrystallization causes modifications to molecular assemblages, which modifies the mechanical characteristics of solids. Saccharin and Nicotinamide coformers of carbamazepine are an example of polymorphic cocrystals. Compared to the first API, these cocrystals tend to be stable [75].

Tabletability

Co-crystallization is suggested to improve flowability and superior mechanical strength, two requirements for tableting. For instance, compared to pure carbamazepine, the co-crystal of saccharine and carbamazepine was shown to be denser. Paracetamol's compression qualities enhanced when theophylline, oxalic acid, naphthalene, and phenazine were present [76].

Applications

Solubility

Cocrystal formation, in which solubility is increased by a conformer of higher solubility, can improve the solubility of low solubility drugs. For instance, the NSAID meloxicam-aspirin cocrystal exhibited a delayed beginning of action (>2 h) with a poor water solubility and high permeability. With the use of cocrystal formulation, the problem was resolved in terms of quicker dissolving, better oral absorption, and a prompt/early start of action. By creating a cocrystal with malic acid, the solubility problem with itraconazole was resolved, and the rate of dissolution was also enhanced [77].

Controlled Release

An advantageous method for adjusting the physicochemical characteristics of pharmaceuticals, such as their solubility and rate of dissolution, is cocrystallization. In particular, the rate at which the API dissolves in water or a buffer solution might vary over time based on the coformer that cocrystallizes with the API. By first going through solvent-mediated phase change, the cocrystals that gave the highest dissolution rates also had the lowest solid-state stability in the same medium [78].

Multidrug Co-Crystal

Multiple drugs Cocrystals are delivery devices that combine many active pharmaceutical ingredients (APIs) into one unit. This tendency is mostly due to two factors: firstly, the necessity to target many receptors for the successful treatment of complicated illnesses such as HIV/AIDS, cancer, and diabetes; and secondly, the growing desire to facilitate the decrease of medication production costs. The multidrug cocrystal is created using the primary cocrystal production procedures [79].

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