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A Brief Review on Pharmaceutical Cocrystals: Advances in Methods of Preparation and Formulation-Based Aspect

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Abstract: **Oral is the most convenient route of drug administration, as it provides numerous advantages over others. In drug discovery, currently the number of drugs with water insolubility has increased, with almost 70% of newly developed drugs showing poor water solubility. Low drug solubility causes sluggish drug absorption, insufficient and inconsistent bioavailability, and toxicity of the gastrointestinal mucosa at the site of absorption. Thus, formulation scientist has a major challenge to make poorly water-soluble drugs more soluble. Several methods have been employed to increase the solubility, dissolution, and further bioavailability of water-insoluble drugsImproving drug dissolving and solubility without affecting their chemical structure is a significant problem. Since most therapeutic medications have structural specificity and about 85% of marketed drugs are crystal products, the crystal structure of the drug is a critical component in determining its efficacy. Therefore, a crystal engineering strategy has been an alternate and possibly effective way of dealing with the problem of low water solubility. Therefore, pharmaceutical cocrystals are one of the most rapidly developing categories of solid medicinal compounds. This review article gives a general review of pharmaceutical cocrystals, advances in their preparation techniques, aspects of cocrystal-based drug formulation, and difficulties encountered during its development.**

Keywords: Cocrystals, Coformers, Poorly water soluble drugs, Solution based methods, cocrystal based drug formulation

I. INTRODUCTION

The oral route is the most convenient route of administration of medicaments, as it has benefits such as ease of drug administration patient convenience, economical, and easily produced on large scale. Oral administration accounts for approximately 60% of developed small-molecule medicinal items in the commercial market. Among all pharmaceutical formulations designed for human use, oral formulations have an estimated 90% of the global market share (Alqahtani et al., 2021). More than 80% of marketed formulations are solid dosage forms intended for oral administration. However, solubility and rate of dissolution are rate limiting factors in determining the efficacy. Additionally, a drug's oral action should be considered. Thus, the drug should have sufficient solubility to get absorbed at the absorption site and to show desired pharmacological action. In drug discovery, in current years the number of drugs with water insoluble has increased, Approximately 70% of newly produced medicines have poor solubility (Kawabata et al., 2011). Low drug solubility causes sluggish drug absorption, inadequate and variable bioavailability, and toxicity of the gastrointestinal mucosa at the site of absorption. Solubility is a crucial rate limiting factor for drugs that are taken orally. As it is a fundamental parameter that controls the rate and extent of absorption and bioavailability of drug (Savjani et al., 2012)(Khadka et al., 2014). Developing an active pharmaceutical ingredient (API) with Suitable solubility and the permeability for oral dosage is crucial for achieving desired bioavailability and pharmacological action (Bandaru et al., 2021). It is prime important to increase the solubility and dissolution profiles of drugs without altering the molecular structure. However, it is a peculiar challenge (Thakuria et al., 2013). Thus, formulation scientist has a major challenge in improving the solubility of insoluble drugs (D. Sharma, M. Soni, S. Kumar, 2009).

According to intestinal permeability and solubility, medicinal compounds are divided into one of four groups by the biopharmaceutical classification (BCS). Among these BCS classification Mainly BCS class II (low solubility and high permeability & class IV drugs (low solubility & low permeability) have always posed a problem in case of enhancing the solubility (Kawabata et al., 2011)(Najar & Azim, 2017)(Mahapatra et al., 2020). Several techniques tend to improve the solubility and dissolution of water-insoluble drugs (Vemula et al., 2010). Since most therapeutic medications have structural specificity and around 85% of marketed medications are crystal in nature, it is crucial for evaluating efficacy (Tiekink, E.; Vittal, 2006) (Liu et al., 2022). Therefore, a crystal engineering strategy is an alternate and possibly effective way to enhance the physicochemical characteristics of medications that are poorly soluble (Table 1) (Nijhawan et al., 2014). This review article offers a thorough review of pharmaceutical cocrystals, covering both traditional and advanced preparation techniques. It also highlights the less-explored aspects of cocrystal-based drug formulations and the hurdles involved in developing products based on cocrystals.

TABLE 1: Reported poorly water soluble drugs cocrystals along with their coformers, method of preparation and their applications

Cocrystal	Coformer	Method of preparation	Application
Ezetimibe	Glycine	Neat grinding method	Improved solubility with faster dissolution (Anand & Nanda, 2022)
Ketoconazole	Fumaric acid and adipic acids	Cooling Crystallization	100-fold increased in solubility (Martin et al., 2013)
Piroxicam	Sodium acetate	Dry grinding method	Indicated higher dissolution rate (P. Panzade et al., 2017)
Meloxicam	Aspirin	Solution, slurry, and solvent drop grinding methods	Improved kinetic solubility and a nearly 12-fold significant reduction of time needed to achieve therapeutic level (Cheney et al., 2011)
Ibuprofen	L-proline	Hot melt extrusion and solvent evaporation	Higher in vitro drug release (Kshirsagar et al., 2022)
Itraconazole	Suberic acid	Spray drying and Rotary evaporation method	~39 times higher rate of dissolution (Weng et al., 2019)
Indomethacin	Saccharin	Supercritical fluid technology	Controlled distribution of particle size and shape cocrystals (Padrela et al., 2009)
Carbamazepine	Nicotinamide	Ultrasound assisted solution cocrystallization	Produce pure cocrystals (Ying et al., 2021)
	Saccharine	Antisolvent Method	Superior quality with enhanced efficiency (Wang et al., 2013)
Resveratrol	4-aminobenzamide and isoniazid	Liquid assisted grinding and rapid solvent removal method	Improved solubility and tabletability (Zhou et al., 2016)
Curcumin	Resveratrol	Supercritical fluid atomization technique	Improved solubility and dissolution and antioxidant properties (Dal Magro et al., 2021)
Telmisartan	Oxalic acid	Slow evaporation and ultrasound-assisted co-crystallization	Improved mechanical properties and dissolution and tablet properties (Ratih et al., 2020)
Theophylline	Urea, saccharine and nicotinamide	Spray drying method	Improved powder physiochemical properties (Alhalaweh et al., 2013)
	Saccharine	Supercritical enhanced atomization process	Lower solubility (Padrela et al., 2014)

II. PHARMACEUTICAL COCRYSTALS

Typically, APIs can form multi-component crystals such as solvates and hydrates. Because an API can be polymorphic. For this, Clinical trials and formulation activities are crucial components of drug development to decide particular solid form of an API for scale-up (Aitipamula et al., 2012),(Karpinski, 2006). To date, the properties of APIs can be altered by applying several solid-state strategies, such as salts, polymorphs, hydrates, solvates, and cocrystals(Aitipamula et al., 2012)(Umeda et al., 2009)(Guo et al., 2021). Whereas these methods have some restrictions; like, salt formation is only applicable to the molecules with appropriate ionizable groups, and hydrates and solvates are frequently unstable because loss of water and solvent molecules over the time. In contrast, cocrystal formation occurs when an appropriate partner molecule (coformer or cocrystal former) is present and any API (regardless of its acidic, basic, or nonionized forms) is used (Guo et al., 2021). Therefore, the cocrystallization category has been one of the most rapidly developing classes of solid medicinal compounds. It has become a useful tool for adjusting physical properties like the solubility, dissolution, and stability of API. The primary benefit of this strategy is that the drugs pharmacological effect does not change. Since it's possible to change an APIs crystal structure to enhance its physicochemical properties over the past two decades, academics and the pharmaceutical industry have paid close attention to it. Along with that, it provides superior chemical stability, purity, and manufacturability relative to the amorphous and liquid forms of formulated drug substances (Sun et al., 2020). The concept of crystal engineering serves as the foundation for the cocrystallization process. The first cocrystal accidentally discovered and illustrated was urea and NaCl in 1783 (Najar & Azim, 2017).

Currently, the engineering of cocrystals has evolved and the cocrystals of APIs and coformers have been termed 'pharmaceutical cocrystals'. This is typically a hydrophobic drug and hydrophilic coformers, which have extremely distinct physicochemical properties including ionization, hydrophobicity, and diffusivity. These characteristics have a significant impact on the dissolving rates of cocrystals (Cao et al., 2016). Since, their physical and pharmacokinetic properties are different compared to pure APIs. Pharmaceutical cocrystals are attracting the interest of formulation scientists (Weyna et al., 2009). Additionally, it provides a novel strategy for dealing with the problem of water insolubility. Some of the reported cocrystals of drugs with poor solubility are briefed in Table 1. Its features are frequently superior than each independent entity since it contains two or more different molecules organized to create a unique crystal form (Savjani et al., 2012).

III. SELECTION OF COFORMER:

There are two main elements of cocrystal structure; one element is an API molecule, and the other is a suitable partner molecule referred to as a cocrystal former or coformer. These coformers are generally selected by considering their nontoxicity for intended use from a list generally recognized as safe (GRAS) (Bandaru et al., 2021). There are diverse choices of coformers. As a result, choosing the right coformer is a key and important step in the designing of cocrystals (Schultheiss & Newman, 2009). So, it's crucial to come up with a screening method that can identify the potential coformers. Over the last few centuries have seen substantial growth in the cocrystals designing and as a result, enough data has been acquired to identify the potential coformers. Some effective methods for screening coformers include the hydrogen bond propensity, Cambridge Structural Database (CSD), supramolecular synthon approach, pKa rule, and Hansen solubility parameter. However, to effectively use cocrystallization in the pharmaceutical company, more effective screening methods must be developed (Kumar & Nanda, 2019). The cocrystallization of a given API with various pharmaceutically approved substances was the first method for coformer selection that was

attempted, but it was ineffective and tiresome and involved trial and error. Following the advent of the CSD, the "supramolecular synthon approach" was effectively used to screen coformers for cocrystal synthesis. The cocrystals strategic development is usually based on supramolecular Synthons. It is an alternative design strategy that identifies supramolecular synthons and is capable of being more focused, quicker, and less expensive. The supramolecular synthon were two types including, Homosynthon having the same functional groups in coformer and API. It formed between carboxylic acid dimer and amide dimer. Heterosynthon having different functional groups in coformer and API. It formed between the carboxylic group and amide the group, between alcohol and ether (Fukte et al., 2014).

IV. PREPARATION OF COCRYSTALS:

Several methods have been developed for the generation of cocrystals. However, choosing the best cocrystallization technique is still being studied. Cocrystal formation methods are characterized as solution-based or solid-based as summarized in Fig. 2. Solution-based techniques require significant quantities of solvent to dissolve cocrystal components. Solid-state techniques offer the ability to eliminate the requirement for solvents, which requires a negligible or no solvent. Moreover, the solvent selection affects the cocrystallization outcomes since an alteration in solvent might vary the API-coformer intermolecular interactions (Guo et al., 2021).

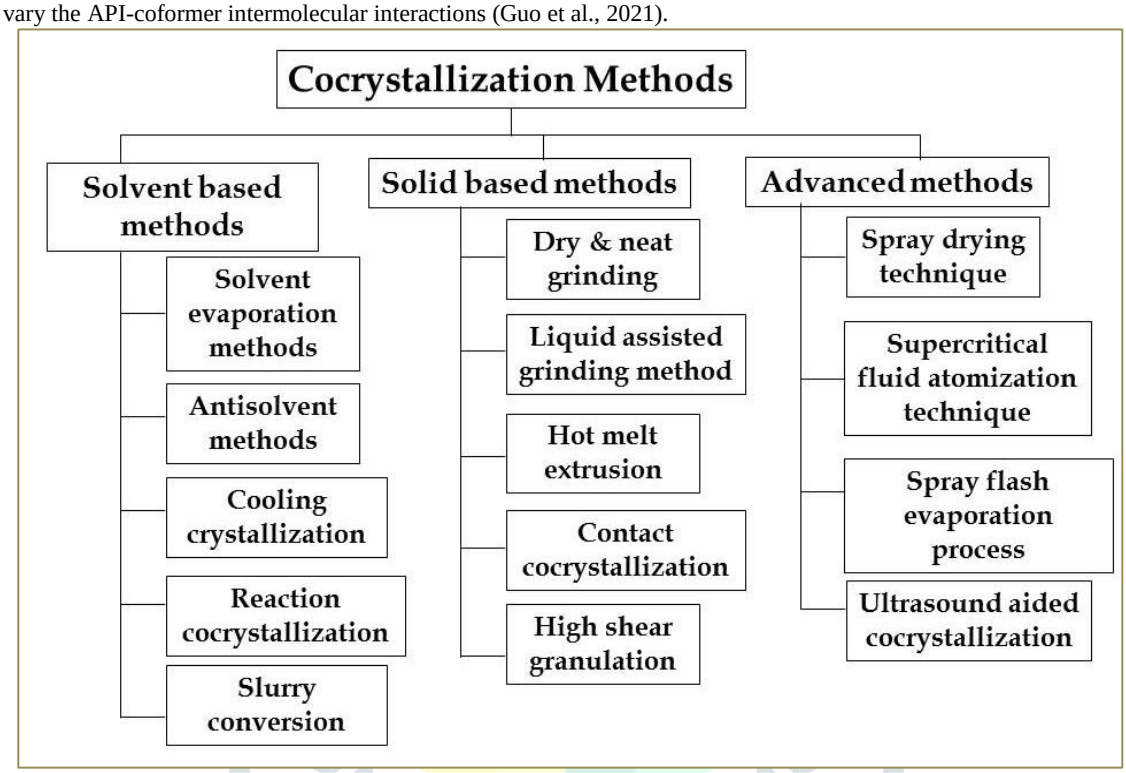

Figure 1: Different methods of cocrystallization

4.1 SOLUTION-BASED METHODS:

These methods are the most popular, straightforward, and easy for processing and regulating, and the end product may be easily controlled. On account of that, these are mostly suitable but restricted to a laboratory-scale preparation of cocrystals. However, the solvent should be selected cautiously as it affects the properties of cocrystals (Bandaru et al., 2021) (Rodrigues et al., 2018). The separations of solvent from the mother liquor and disposal or recycling of solvent are the limitations (Pawar et al., 2021). The success of this method depends on the cocrystal component solubility. Depending on the cocrystal component's solubility, these are broadly categorized as whether a cocrystal system is congruently saturated when the solubility of its constituent parts is similar or incongruently saturated. Where the cocrystal components exhibit dissimilar solubility (Qiao et al., 2011). Several cocrystal production techniques have been examined, depending on the extent of congruency indicated by cocrystal components in terms of solubility. The ternary phase diagram (TPD) and phase solubility diagram (PSD) has been stated in the literature to represent the equilibrium between cocrystal components and cocrystallization solvent (Childs et al., 2004).

4.1.2 Solvent Evaporation Method:

Solvent evaporation is the most common approach for producing cocrystals. It is extensively used to generate superior-quality single-crystal cocrystals. These are suitable for characterization through single-crystal X-ray diffraction. In this method, cocrystal components are dissolved at a suitable stoichiometric proportion in a feasible solvent and then remove the solvent by evaporation to get the cocrystals (Weyna et al., 2009). A slow evaporation rate is typically selected to ensure the production of a few numbers of larger crystals over a great number smaller crystal. Additionally, to ensure the entire restoration of clean cocrystals, individual crystals or the whole crystal sample must be isolated before the solution dries (Buddhadev & Garala, 2021). Additionally, the cocrystallization is influenced by solvent choice, which may affect the reactant solubility. The cocrystal constituents need to be consistently soluble in specified solvent. Otherwise, components may precipitate and cocrystal formation may fail (Guo et al., 2021). According to the literature, this method is utilized to generate many cocrystals. After slowly evaporating acetonitrile for 3 to 5 days at room temperature, a single block-shaped crystal of febuxostat-piroxicam cocrystal was obtained. Which demonstrated better solubility and increased tabletability in contrast to free drugs (Modani et al., 2020). Another study discovered that after just 5 minutes, the fluoxetine HCl: succinic acid cocrystal water solubility had increased by about threefold (Childs et al., 2004).

4.1.3 Antisolvent method:

The antisolvent method is also known as the vapor diffusion method. In this method, antisolvent is expoited to obtain high-quality cocrystals with controlled particle size. This is an efficacious approach to controlling the properties of cocrystals, quality, and particle size. The semi-batch or continuous manufacturing processes is usually carried out for crystallization (Wang et al., 2013). This process involves solubilizing API and coformer in a solvent, then adding a miscible antisolvent to achieve supersaturation and precipitate cocrystals. In cases when the cocrystal has poor solubility, it is pertinent to select the appropriate miscible solvent combination. Since the iclusion of antisolvent reduces cocrystal solubility and causes supersaturation, leading to precipitation (Guo et al., 2021). Wang IC, Lee MJ, *et al*., reported that the cosolvent ratio and the coformer/drug ratio could also significantly influence cocrystal purity and solid output (Wang et al., 2013). This approach also allows for

the creation of nanoscale cocrystals. This method was employed to create drug crystals with limited water solubility, resulting in increased bioavailability and dissolution (Pawar et al., 2021).

4.1.4 Cooling crystallization:

This crystallization method is widely employed to produce large, pure crystals. Several studies indicate that this technique is beneficial for scaling up cocrystal manufacture (Guo et al., 2021). This technique involves cooling a heated solution containing the cocrystal former and drug, which causes cocrystals to precipitate (P. S. Panzade & Shendarkar, 2020). Whereby critical factors that can influence cocrystallization include solvent choice, determining the stable thermodynamic cocrystal operating range, and de-supersaturation kinetics (Buddhadev & Garala, 2021). Moreover, local supersaturation influences crystal properties such as polymorphism of crystal, purity, shape, and distribution size. The process components of mass and heat transformation define this value. As a result, throughout the cocrystallization process, these variables must be properly controlled following various solid-liquid equilibria (Zai Qun Yu, Pui Shan Chow, 2010). By employing a continuous oscillatory baffled crystallizer, 99% pure, homogeneous particle sizes cocrystals of α-Lipoic acid-nicotinamide with kilogram yields were obtained (Zhao et al., 2014). The several modified versions of this approach include the vacuum cooling crystallizer, scraped surface cooling crystallizer, and continuous cooling crystallizer (Bandaru et al., 2021).

4.1.5 Reaction cocrystallization:

This approach of cocrystallization applies to cocrystal components with varying solubilities behavior for cocrystal formation. Mixing reactants in a non-stoichiometric ratio creates cocrystal supersaturated solutions, leading to precipitation. Consequently, the capacity of reactants to reduce the cocrystals solubility governs the nucleation and development of cocrystals (Zhao et al., 2014). This cocrystallization method is potentially used for the effective and rapid process for creating cocrystals at ambient temperature. Additionally, it offers significant advantages over traditional cocrystallization methods including the ability to develop rational in situ techniques for high speed screening of cocrystals. Furthermore, it is more environmentally friendly and easy to transfer into larger-scale cocrystallization processes (Rodríguez-Hornedo et al., 2006). By using this method several cocrystals were prepared, carbamazepine-saccharin cocrystals (Cao et al., 2016), and indomethacin-saccharin cocrystals (Rodríguez-Hornedo et al., 2006).

4.1.6 Slurry conversion method:

In the crystallization method cocrystals can be generated regardless of the stoichiometric ratio of the components of cocrystal. To create this suspension, API and suitable conformers are combined with various solvents. After the solvent is removed, the solid material is dried for five minutes with a nitrogen flow before being PXRD characterized. As soon as drug and cocrystal former are stable in the solvent, cocrystals can be created using this method (Buddhadev & Garala, 2021) (Douroumis et al., 2017). Since this is a phase transformation that is mediated by a solution, extra cocrystal components must be introduced to the solvent. The gradual dissolution and generation of a complex of each component then accelerate the nucleation and cocrystal growth. Because of the drop in reactant concentrations brought on by cocrystal formation, the reactants must be undersaturated to continue dissolving the cocrystal component. The ternary phase diagram, which serves as a guide for cocrystal supersaturation, determines the operational range of the components concentration and temperature (Guo et al., 2021). According to Huang *et al*., the operating temperature and starting component concentration have a substantial impact on the rate of theophylline-benzoic acid cocrystal formation, which is identified by in-line Raman spectroscopy. Because a higher starting concentration might increase the likelihood of components collision and total contact surface area, the reactant concentration and temperature demonstrated a positive association with the rate of cocrystal formation. Conversely, an increase in temperature enabled the reactants to reach the activated state more rapidly (Huang et al., 2019). Ahuja *et al*. have revealed three novel cocrystals (sulfamethazine-nicotinamide, sulfamerazine-salicylamide, and sulfamerazine-anthranilic acid) utilizing these technique. The authors noted that the cocrystallization rate increased when the heating source was a microwave (Ahuja et al., 2020). Utilizing acetone as the solvent, researchers used the isothermal slurry conversion crystallization method to prepare sacubitril and valsartan cocrystals (Zhang et al., 2021).

4.2. SOLID-BASED METHODS:

These methods are viable substitutes for solution-based methods. As these processes produce cocrystals with negligible or no solvent, they are efficient and environmentally beneficial. Cocrystal formation occurs naturally through physical contact or pulverizing with intense energy inputs. However, this approach has certain drawbacks, including inadequate control of cocrystal properties and limited applicability to thermolabile pharmaceuticals (Pawar et al., 2021).

4.2.1 Contact cocrystallization:

After "softly" mixing the raw materials, the API and coformer interactions can proceed independently (Guo et al., 2021) (Nagapudi et al., 2017). It has been observed that mixing pure API with coformer under-regulated atmospheric conditions results in the spontaneous production of cocrystals. Cocrystallization takes place without the use of any mechanical forces (Buddhadev & Garala, 2021). The potential process for spontaneous cocrystallization includes moisture sorption, eutectic phase formation, amorphization, and long-range anisotropic molecular transport (Kaupp, 2003). The cocrystallization rate for pre-milled reactants was proven to be much higher than that for unmilled reactants. Consequently, the pure components may have individually been completely pulverized before combining in some circumstances. Additionally, at greater relative humidity and temperatures increased cocrystallization rates for some systems have been observed despite any mechanical stimulation (Kumar & Nanda, 2019).

4.2.2 Neat grinding:

Recent interest in grinding and cocrystals can be traced to the 1980s, when Etter *et al*. stated that dry grinding, also called neat grinding. This approach is effective for creating cocrystals of methyladenine and methylthymine (Weyna et al., 2009). It is easy and enables fast synthesis of the required cocrystal. This method consists of combining two or even more coformers in a fixed stoichiometric ratio and grinding them either physically with mortar and pestle or mechanically with a ball mill or vibrator mill for a particular period (Garg & Azim, 2021). Usually, the typical grinding time ranges from 30 to 60 min. The grinding results in the particle size reduction which increases the specific surface area and interaction between the materials that helps in the intermolecular bonds formation. The mechanism behind cocrystallization by grinding involves molecular diffusion, eutectic formation, and an amorphous phase followed by cocrystallization. However, this approach has certain limitations, comprising the inability to produce a cocrystal, partial conversion to the cocrystal, and crystalline flaws with the capability to produce some amorphous content. To achieve a pure cocrystal product, more purification procedures are required in neat grinding (Friščič & Jones, 2009).

4.2.3 Hot melt extrusion (HME):

Hot melt extrusion is a single-step, scalable, and continuous process, and widely used for cocrystal production. Moreover, it is a solvent-free method and is therefore often regarded as a greener method. Additionally, it is applicable for APIs that are unstable in the condition of water and oxygen. As the final product may contain a negligible quantity of oxygen and water owing to the solvent-free nature of the process. Using heat

and pressure exceeding melting temperatures, this approach quickly blends the API and coformer. The melting of components results in intimate mixing. Cocrystals develop directly in the melt and are continually extracted from the extruder as pure extrudate. Nowadays, this technique replaces old methods to manufacture cocrystals as it has key advantages, it is more efficient than conventional approaches, has minimal residence time, are organic solvents free, reduced waste, and is a combination of intense mixing and controlled temperature (Patil et al., 2016). The main problem of this approach is the possibility that significant shear stress and strain generated during processing will cause an active medicinal component to deteriorate chemically. Additionally, it consumes high energy and accelerates extruder wearing (Bandaru et al., 2021) (Patil et al., 2016)(Fischer et al., 2014).

4.3.4 Liquid-assisted grinding (LAG):

The method was originally termed solvent drop grinding. It is a slight deviation from a neat grinding method as there is the inclusion of a little amount of solvent which gets exhausted during the cocrystallization reaction. This solvent catalyzes facilitating cocrystallization by enhancing molecular diffusion or acting as a crucial aspect that develops a multi-component inclusion framework. Liquid-assisted grinding produces cocrystal products with higher yields and crystallinity than neat grinding. Additionally, this approach is ideal for quick cocrystal scrutiny and does not depend on raw material solubility. It includes combining the two components with a very little quantity of solvent (As an instance, a few hundredths of a solvent equivalent per mole of the component) to significantly enhance the kinetics of cocrystallization. The choice and quantity of liquid are crucial factors in the mechanochemical process, affecting the quality of crystals and the production of various solid products (Fischer et al., 2014).

4.3 ADVANCED METHODS:

4.3.1 Spray drying technique:

During spray drying, a stream of hot air quickly evaporates the solvent from a solution or suspension, resulting in dry particles. Because it is a rapid, persistent, a single-step approach, it is commonly applied technologies for material processing and scale-up in the pharmaceutical and food sectors. Few drug materials are created in crystalline forms (polymorphs or solvate or hydrate), even though the solid-state nature of the spray-dried materials is frequently amorphous due to quick solidification. To produce polymorphs or metastable crystalline forms by spray drying, it is thought that the solution must quickly become supersaturated and the temperature must shift. Consequently, spray drying seems to provide a special setting for the synthesis and scale-up of cocrystals. However, spray drying techniques disregard the confinement of the stability zone in the phase diagram during cocrystal formation. Therefore, it can have significant advantages in scale-up operations over equilibrium methods, which require a extensive knowledge of phase behavior and considerable effort in control and optimization of the process. This method can also produce crystals embedded in an additive matrix with better rheological properties. To modify the solvent evaporation approach in the drug-coformer incongruent solubility system, spray drying cocrystallization can be used when pure cocrystal production is not attainable. This method is both innovative and reliable for large-scale production of cocrystals (Vehring, 2008). Amjad Alhalaweh and Sitaram P. Velaga demonstrate that the process of spray drying can be used to produce new or even pure cocrystals (Alhalaweh & Velaga, 2010).

4.3.2 Supercritical fluid atomization technique:

This approach uses supercritical solvents to achieve cocrystallization, taking use of their solvent properties. As it is being eco-friendly solvent, reduces the processing steps, is beneficial to get solvent-free finished products, increased solubility, and due to low temperature (31°C, 7.39 MegaPascal) suitable for thermolabile drugs (Douroumis et al., 2017). Generally, supercritical CO_2 is used for this technique. The slurry of drug and the coformer is prepared by suspending it into supercritical CO_2. After that, the system is swiftly depressurized to atmospheric conditions, causing the quick expansion of supercritical CO_2 solutions. That result in substantial supersaturation of the solute in the depressurized supercritical CO_2 due to the quick loss of the solvent power of the fluid. Due to the rapid supersaturation, the fine particles are eventually forced to precipitate. This causes nucleation and crystallization. This process uses highly volatile, non-toxic solvents, leaving no solvent residues in the finished crystals. The limited product yields and low solubility of drug coformer pairs in supercritical CO_2 are drawbacks of this method(Padrela et al., 2015). The curcumin-resveratrol cocrystal produced by using this method has increased solubility and dissolution and antioxidant properties compared to raw components. Which leads to increase in the antinociceptive or anti-inflammatory potency of curcumin could be due to its bioavailability improvement (Dal Magro et al., 2021).

4.3.3 Spray flash evaporation process:

Spray flash evaporation is a technique used in explosives to create semi-crystalline nanocomposites by using the flashing effect of superheated fluids under rapidly pressure drop. The process comprises atomizing the materials into a chamber by a hot hollow cone nozzle, dissolving them at a low boiling solvent (60°C), followed by over pressurization at 40-60 bars. The sudden fall in pressure causes thermodynamic instability in the superheated solution, and the extra energy turns into latent energy, causing the molecules to crystallize (Buddhadev & Garala, 2021). The sudden drop in spray liquid pressure in an already heated large chamber is the main bedrock of this method. The substances under study were dissolved in (acetone) solvents with a boiling point below 60° C in a stoichiometric ratio. First, a temperature of 70° C is applied externally to the chamber. To establish a low-pressure area and increase the temperature of the air inside the chamber. A single fluid hollow cone nozzle with a 0.3 mm diameter and an ultra-high purity (UHP) nitrogen overpressure of 75 kg/cm^2 was then used to nebulize the solution inside the chamber. The thermodynamic equilibrium is disrupted by a quick reduction in liquid pressure in a hot environment, which makes the liquid droplets unstable. The solvent can evaporate quickly because the extra thermal energy is transformed into latent heat to restore stability. The quick elimination of the solvent causes solute molecules to arrange into optimal lattice sites, resulting in a crystalline material. The crystal's stoichiometric ratio of both solutes within the same lattice would leads in a cocrystal formation (Ghosh et al., 2020).

4.3.4 Ultrasound-aided cocrystallization:

Recently, ultrasound has been exploited to produce cocrystals from a suspension or solution, or slurry (Childs et al., 2004). Ultrasound can produce cocrystals from a solution containing cocrystal ingredients. However, it is hard to form cocrystals from a solution comprising cocrystal components with varied solubility behavior, resulting in a non-congruent cocrystal component system. Therefore, it is preferable to achieve the solubilization of non-congruent cocrystal components during cocrystallization using ultrasonic energy. It is widely acknowledged that ultrasound modifies the ternary phase diagram region by shortening the induction period and narrowing the metastable zone. There are numerous examples proving the assistance of ultrasound in the crystallization of a single component from a solution at high concentrations (20-40 l/mg). With this in mind, ultrasound-assisted cocrystallization from solution can be expected to generate pure cocrystals (ultrasound-assisted solution cocrystallization, USSC). The existence of cavitation energy from ultrasonic waves has an impact on nucleation from particle-free solution when ultrasound is applied to a solution. By shortening the induction period and narrowing the metastable zone, this cavitation event can induce primary nucleation at lower supersaturation values. The use of ultrasonography is more effective in achieving supersaturation levels (Aher et al., 2010).

V. ASPECT OF COCRYSTAL-BASED DRUG FORMULATION:

Although there are several studies on designing, synthesizing, and characterizing cocrystals, but it lacks data based on cocrystal-based drug formulation. Cocrystals can improve physicochemical properties of the drug without affecting their pharmacological action. It has caused a surge of interest in these entities as potential alternatives for salts and polymorphs with additional advantages. Although, the strategy of cocrystals seems straight forward. But, the formulation of it into an effective dosage form is very challenging (Yousef & Vangala, 2019). During the designing of an effective dosage form the cocrystal and excipients interactions were documented in the literature.

5.1 Unintentional cocrystal formation in the formulation:

As pharmaceutical excipients or additives play a vital role during developing dosage form. These are added during formulations and may act as bulking agents, assist in the operating of the API during the manufacturing, or play a vital function in stabilizing the pharmaceutical product, or they may bring organoleptic attributes to the formulation or facilitate drug absorption, bioavailability, and other pharmacokinetic considerations. Some reports have shown that during formulation certain excipients can unintentionally form cocrystals in the dosage forms (Yousef & Vangala, 2019). In whole tablets, the cocrystallization of the drugs carbamazepine (CBZ) and nicotinamide (NMA) is caused by the release of crystallization water during the evaporation of dibasic calcium phosphate dihydrate (DCPD) (Arora et al., 2011). Therefore, the preformulation study of cocrystal based pharmaceuticals can be a prerequisite factor during the development of cocrystal-based drug formulations.

5.2 Reported Cocrystals Formulation:

5.2.1 Cocrystals of carbamazepine-succinic acid (CBZ-SUC): In this study, the intrinsic dissolution rate (IDR) was employed as a tool to develop tablet formulations for soluble cocrystals of carbamazepine and succinic acid formed via slurry crystallization. Utilizing three distinct polymers, soluplus (F1), kollidon VA/64 (F2), and hydroxypropyl methylcellulose acetate succinate, three tablet formulations of carbamazepine-succinic acid cocrystal were produced (F3). It was investigated whether tablet formulations could stabilize the cocrystal at hastened conditions of 40°C and 75% relative humidity (RH) as well as during a dissolution study. It was explored if using polymers will significantly increase the IDR of CBZ-SUC cocrystal. The effective selection of the appropriate polymer level for the formation of stable tablet formulations of weakly water-soluble CBZ is assisted by IDR data. The KollidonVA/64 based tablet formulation outperformed the other two, and all three formulations demonstrated enhanced *in vitro* and *in vivo* efficacy above the commercial CBZ tablet (Ullah et al., 2016).

5.2.2 Mefloquine Hydrochloride (MFL) Cocrystals: In this study, the effectiveness of Mefloquine Hydrochloride (MFL) Cocrystals in tablet formulation was examined. The MFL cocrystals were combined with various ratios of cocrystal formers in tablet form, and their effectiveness was assessed. Comparing cocrystal-based tablets to pure MFL tablets; the rate of dissolving was improved (Shete et al., 2013). It was extensively observed that caffeine-oxalic acid cocrystals dissociate in the vicinity of a different of pharmaceutical excipients yet maintain stability across range of temperature and humidity conditions (Duggirala et al., 2020).

5.3 Reported challenges in cocrystals formulation:

Recent studies highlighted the impact of drug-excipient interactions on the design of robust formulations containing cocrystals. A majority of the pharmaceutical cocrystals shown in the scientific studies are comprised of acidic coformers, and there is a potential for cocrystal dissociation due to the water sorption potential of basic excipients followed by the ionization of the coformer. Normally, a pharmaceutical cocrystal tends to undergo dissociation, and unintended dissociation especially at inappropriate temperatures and under high relative humidity conditions turns to the corresponding free API and coformer. Therefore, it is needed in today's era to study aspects related to cocrystal-based drug formulation.

5.3.1 Ertugliflozin L-pyroglutamic acid cocrystal: Ertugliflozin (ERT), an oral sodium-glucose cotransporter-2 inhibitor has been approved both as monotherapy and fixed-dose combination therapies with dipeptidyl peptidase-4 inhibitor, sitagliptin (Steglujan), or common first-line therapy for the cure of diabetes, metformin. Under conditions of elevated temperature and humidity, the neat cocrystal of ertugliflozin L-pyroglutamic acid (ERTLPG), marketed by the commercial name Steglatro®, is physically stable. But dissociation of cocrystal, or the development of the free amorphous form of ERT, was seen at 30°C/75% RH for a week while being accompanied by certain excipients. The impact of excipients physicochemical properties on the cocrystals physical stability was examined to develop an understanding of the mechanisms of cocrystal dissociation in the tablet. The dissociation of the cocrystal was facilitated by raise in pH of the binary solution (cocrystal + a class 4 excipient) or in the aqueous cocrystal layer which is sorbed on the exterior surface of a hydrophobic excipient of class 3. The surface acidity of the excipient facilitates ERTLPG cocrystal dissociation in the vicinity of a basic excipient and is catalyzed by water as a solution-mediated mechanism. Covering the cocrystal with non-polar silica and incorporating a pH-lowering chemical into the formulation can both help to slow down the dissociation process. The dissociation was absent in coated cocrystal (formulation F4) at accelerated conditions (40° C/75% RH) for four weeks (Duggirala et al., 2020).

5.3.2 Sacubitril and valsartan cocrystals: In this study, the cocrystal of sacubitril (SAC)-valsartan (VAL) was considered as a model (Entresto® tablet). The impact of various polymeric additives on cocrystal formulations was studied. The impact of drug-excipient interaction on the drug's performance in biological systems was also explored. In cocrystal formulations, polymeric additives such as polyvinyl pyrrolidone (PVP), hydroxy propyl cellulose (HPC), and hydroxy propyl methyl cellulose (HPMC) were chosen. The effcet of polymeric additives on intermolecular interaction, drug dissolution, and permeation along with *in vivo* performance of the drug was assessed. They found that certain excipients, particularly polymers, can compete with the intermolecular hydrogen bonding between cocrystal components and give unusual affinity, so enhancing the therapeutic advantages. The Entresto® tablet's coating excipient, HPMC, prevented the drug from supersaturating as intended, which resulted in suboptimal cocrystal oral absorption. In contrast, PVP appeared to support and help in maintaining drug supersaturation, leading to improvements in drug bioavailability (Zhang et al., 2021).

VI. CONCLUSION:

The pharmaceutical cocrystal is among the top rapidly developing categories of solid medicinal compounds. It is becoming an effective technique for modifying the solubility, stability, and several physicochemical parameters of drugs without changing their pharmacological effects. The selections of coformer, scaling up to multikilgram scale are the main barrier to commercialize the pharmaceutical crystals. While formulating the pharmaceutical cocrystals, it is necessary to critically analyze studies on pharmacokinetic characteristics, therapeutic efficacy and stability, toxicity concerns, and interactions between cocrystals and other additives. More concentrated research on the formulation properties of cocrystal-based drugs are required. Thus, this review article provides a detailed overview of the need for pharmaceutical cocrystals, the selection of coformer, and traditional and advanced preparation methods. Further, it highlights on formulation features of cocrystal-based drugs which is the least reviewed portion of it. Therefore, for the efficient treatment of disease in the patient, more pharmaceutical crystals must be produced and commercialized to provide safe and effective solid oral cocrystal-based formulations.

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