A Review on Solubility Enhancement Technique of BCS Class II Drug by Co-crystallization Method

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Abstract

Poor aqueous solubility of a drug is an industry wide issue for pharmaceutical science in dosage form and development. Many numerous approaches have been developed for solubility enhancement of biopharmaceutical class II drugs (low solubility and high permeability). Therefore, the improvement of drug solubility there by its co-crystallization method. Design and synthesis of pharmaceuticals co- crystals have entered great interest in the recent times. Co crystallization of medication substances offer a tremendous occasion for the development of new medication products with superior physical and pharmacological properties similar as solubility and bioavailability. This short review summarized the current trend for co crystal formation using the different of co-crystallization method.

Keywords: - *Solubility, solubility enhancement, bioavailability, co-crystal, co-crystallization.*

1.Introduction

Solubility improvement for hydrophobic medicines is an important pharmaceutical way in expression growth to achieve their high bioavailability and remedial exertion at target points [1]. Around 40 – 60% of new chemical entities (NCEs) suffer from the problem of poor water solubility and hence poor bioavailability issues, making medicine solubility and bioavailability improvement as two important demurrals constantly encountered during expression progression steps [2]. According to biopharmaceutical Classification Systems (BCS) of drugs, Class II and IV drugs suffers the most and require special attention in terms of solubility and bioavailability enhancement [3]. A number of methodologies can be acclimated to enhance solubilization of poor water solvable medicine and farther to enhance its bioavailability. The ways usually employed for solubilization of medicine includes micronization, chemical variation, pH adaptation, solid dissipation, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of inadequately solvable medicines is a constantly encountered demurral in web studies of new chemical realities as well as in expression design and progression [4,5]. Among these varied approaches, one of the unique approaches is co-crystallization-a multi component system conforming of medicine and co-former, bound together with noncovalent relation in a finite stoichiometric rate [6,7]. Drugs that have low solubility are biopharmaceutics class system (BCS) class II drugs. so, increasing the solubility of BCS Class II drugs also increases their bioavailability [8].

BCS (Biopharmaceutics classification system) classify the drug in to four classes according to their solubility and permeability.

BCS Classes	Solubility	Permeability	Absorption pattern
Class I	High	High	Well absorb
Class II	Low	High	Variable
Class III	High	Low	Variable
Class IV	Low	Low	Poorly absorbed

Table1: Biopharmaceutical Classification System [9]

1.1 Need for solubility enhancement

Oral medication delivery is the most practical and preferred mode of administration due to its convenience of administration, high patient compliance, cost effectiveness, lack of sterility contaminants, and flexibility in the creation of dosage forms. Slow medication absorption from poorly soluble drugs results in insufficient and inconsistent bioavailability. Solubility is a vital parameter to attain asked drug attention in systemic circulation for attaining necessary pharmacological response. The solubility and bioavailability of medication determine how well it works therapeutically. Only 8% of currently novel drugs at this, time have

high solubility and permeability. The basic aim of formulation and development section is to make that medication available at proper site of action within optimum dosage, thus needs to be improve by various solubility enhancement technique [10].

2.Co-crystal

Cocrystal technology emerged as a new approach because of its success in overcoming the problem of insolvable medications [11]. Cocrystals are solid materials crystallized from two or more different factors with a stoichiometric rate at room temperature that are bound by noncovalent bonds, generally hydrogen bonds [12]. Pharmaceutical co-crystallization is an accurate way for changing the chemical and physical properties of the medication without affecting its therapeutic effects. Pharmaceutical co-crystallization is an accurate way for changing the chemical and physical properties of the medication without affecting its therapeutic effects. Cocrystals have increased medication solubility because of the lower lattice energy and higher affinity of the solvent [11]. Fig 1. gives the idea of co-crystal preparation.

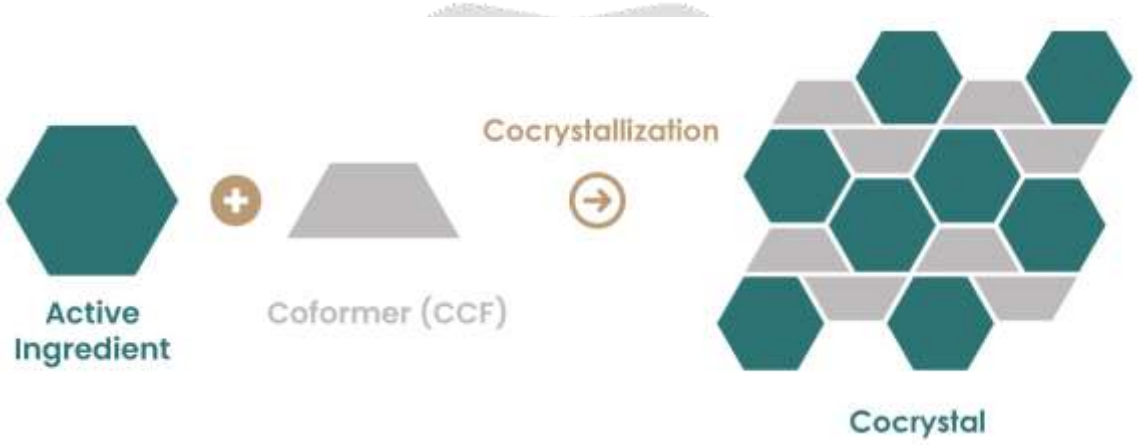

Figure 1. Classical diagram illustrating co-crystal preparation

2.2 Selection of co-former

Basically, co-former that used for co-crystallization process must be a nontoxic or GRAS (Generally Regarded as Safe) compound [13]. There are three kinds of theories that can be used for co-former selection medicine synthon approach, pKa approach, and solubility approach. Pharmaceutical synthon proposition explained that co-former must have reciprocal functional groups to functional groups of medicines [11].

Another theory for conformer selection based on differences of pKa values between medicine and co-former, namely as Rule of Three, which state that differences of drug and co-former pKa values, lower than zero will produce cocrystal, and lower than 3 is a slate area where either cocrystal or swab can form [14,15]. The newest theory, still, proposed that sea will be formed when medicine and co-former have pKa value differences ΔpKa> 1 or cocrystal will be formed when ΔpKa [16].

3.Method Cocrystal Preparation

To date, wide approaches have been established for cocrystal preparation, similar as solid- state grinding, solution reaction crystallization, solvent evaporation, slurry conversion and hot melt extrusion. still, the choosing of an able co-crystallization system remains empirical. Generally, the most extensively used cocrystal conformation approaches can be classified as solution-methods and solid- based methods (Fig 2.) [9].

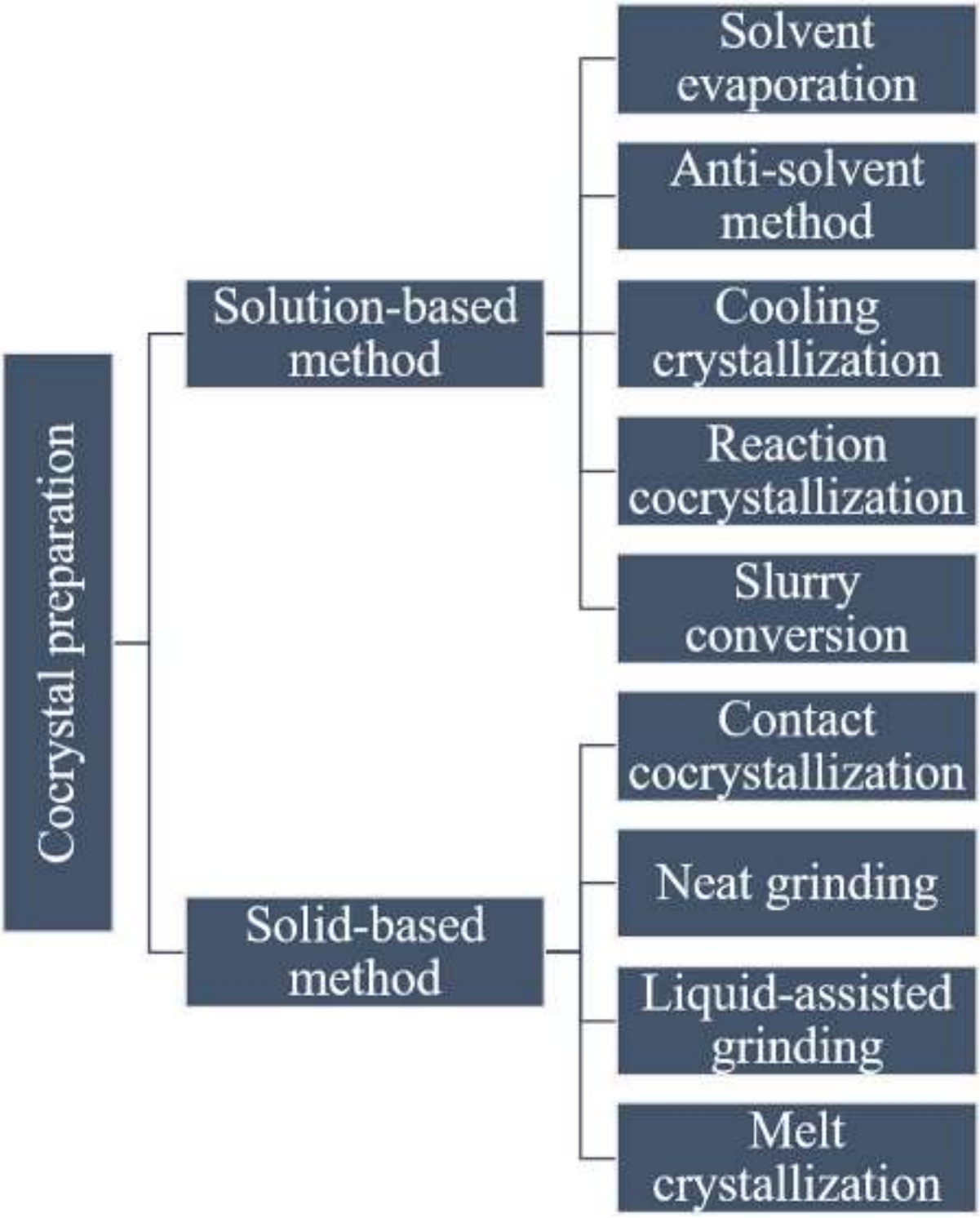

Figure 2. Common method of co crystallization preparation

3.1. Solution-based methods

3.1.1. Solvent evaporation method

This method is frequently applied in the cocrystal preparation process. This method involves dissolving the drug material and co-former in a single solvent and allowing the solvent to evaporate more slowly. The method is based on the idea that a complementing co-former and a beneficial medicinal component can form a hydrogen bond [18].Due to its simplicity and efficiency, this is a widely used experimental screening system for cocrystal formation [19].

3.1.2. Antisolvent method

This process, also known as vapour diffusion, produced cocrystals with a pure grade. In this method, an antisolvent was added to the solution in which the API was either insoluble or low solubility when an anti-solvent was introduced. When the second solution was introduced to the first antisolvent, a supersaturation was observed. Using this technique, an antisolvent was selected and within this the rate of solubilization of API was 2:1 (API as an antisolvent) and then another either a solvent or an antisolvent was selected to the after that, the co-former was dissolved at 40.0 at a temperature of ± 0.5 °C the solvent was combined, producing the precipitation of the medication as cocrystals, then wash the vacuum-filter the crystals. three times with distilled water, and then let it dry at room temperature [20,21].

3.1.3. Cooling crystallization

The drug gets recrystallized by changing the result temperature via super saturation. A sufficient quantity of medicine is dissolved at40.0 ±0.5 °C in a certain amount of detergent. By nonstop shifting, (0.25 °C/ min) the solution is also cooled in the water bath to10.0 ±0.5 °C. After vacuum filtration, the chargers are washed with distilled water and dehydrated for 24 hr at room temperature and also placed in desicators [22].

3.1.4. Reaction co-crystallization

When the cocrystal components have various solubilities, reaction co-crystallization is appropriate for cocrystal formation; reactants with nonstoichiometric concentrations are combined to produce cocrystal supersaturated solutions, which result in condensation of cocrystals. Using this technique, cocrystal nucleation and growth are determined by the reactants' capacity to make cocrystals less soluble [23]. The Meloxicam-salicylic and carbamazepine-saccharin cocrystal formation and reaction crystallisation method has produced indomethacin-saccharin cocrystals. [24,25,26].

3.1.5. Slurry conversion

By adding the solvent to the mixture of cocrystal materials, which dissolves, mixing the solution with the aid of an appropriate mixture, and allowing the solvent evaporate at room temperature, the amount of drug and co-former ratio was determined based on stoichiometric ratios. The material selection for this approach needs to be stable in the solvent, and it has the limitation of requiring more solvent and time for completion [27,28,29,20].

3.2 Solid-based methods

3.2.1. Contact co-crystallization

conformation of cocrystals under a regulated atmospheric condition through the mixing of pure API and co-former. In this process, during co-crystallization, no mechanical forces are applied. still, short grinding of pure factors collectively until mixing has been performed in some instances [30,31,32].

3.2.2. Solid-state grinding

Solid- state grinding is another technique that has been used for numerous times in the field of exploration for the medication of cocrystals, espousing this methodology, liquid assisted grinding (Pause) in the solid state was employed to examine the product of diastereomeric cocrystals of malic and tartaric acids [33]. This approach follows two different approaches for the medication of molecular assemblies, similar as the neat or dry grinding (DG) system and LAG system.

3.2.3. Neat grinding

Grinding method have been widely used for the co-crystal conformation over the once many times and found to be superior than other method (results or melt). Grinding ways are of two types neat or dry grinding and wet drying. In neat grinding, API and conformer are mixed together in a stoichiometric rate and predicate them by using either mortar and pestle or ball mill. In Wet grinding was performed in an analogous manner that of neat grinding by addition of some drops of solvent in the mixture [34].

3.2.4. Liquid-assisted grinding

Liquid- assisted grinding involves the grinding of the API and the co-former simultaneously, along with the addition of a nanosecond volume of solvent (generally many tenths of one like of solvent per operative of starting accoutrements). The solvent acts as a catalyst but isn't affected in the end product. The advantages are advanced rate of conformation of cocrystal, advanced yield, and precise control over the metamorphosis of API into its polymorphs, better product crystallinity, and connection to a variety of co-crystal formers. The system enhances the selectivity of the co-crystallization. This system avoids inordinate use of detergent and is regarded as a “green” process [35].

3.2.5. Melting crystallization

Hot melt extrusion (HME) is a relatively new addition to the cocrystal preparation possibilities. This specialized method incorporates the co-former and the target molecule's simultaneous melting and blending through the use of a heated screw extruder.

The starting components are typically combined and fed into the heated extruder in a molar ratio. Melting takes place, which makes it easier to mix the initial ingredients properly. The cocrystal nucleates initially in the melt, and it is continuously removed from the extruder as pure cocrystal extrudate. The technique offers several advantages over solution-based procedures, including reduced waste, faster running times, enhanced conversion, and the elimination of organic solvents. Additionally, the system is well-suited for continuous pharmaceutical manufacturing [30,36,37].

3.3. Miscellaneous Methods

3.3.1. Laser Irradiation

This method consists of using a high-power CO2 laser to irradiate powder blends of co-crystal formers and induce their recrystallization to a co-crystal structure. Titapiwatanakun et al. have used this method to produce caffeine co-crystals with oxalic acid and malonic acid. Interestingly, these authors have found that the co-crystal formers need to sublime to a considerable extent for the co-crystallization to take place, which indicated that the mechanism of the molecular rearrangement between API and co-former molecules and the nucleation of the cocrystal is likely to take place in the vapour phase [38].

3.3.2. Resonant Acoustic Mixing

Resonant acoustic mixing has been used to mix the target molecule and co-former in the presence of a liquid to form a co-crystal in the absence of any grinding media. In this system, mechanical energy is transferred acoustically into a wet down greasepaint admixture, encouraging intimate mixing of the factors. A range of carbamazepine co-crystals were successfully produced using a lab RAM reverberative acoustic mixer operating at 80 −100 G and 60 Hz. The co-crystal products were separated at a range of laboratory scales, 100 mg and1.5 and 22 g, and the technology appeared amenable to scale- up [38].

3.3.3. Freeze-Drying

Freeze-drying, technically known as lyophilization, has been largely used as a processing method to save a wide variety of products, which include food and medicaments. This process works by solidifying the material and also reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. It has also has been demonstrated lately to be a doable system for the medication of new solid forms of co-crystal systems [38].

3.3.4. Electrospray Technology

Electrospray Technology The electrospray co-crystallization of carbamazepine and itraconazole [39], developed with the desired conformer, discovered that the electrospray approach is a unique approach which is a single- step, particular system for the conflation of cocrystals, which leaves the traditional methods far before. This approach involves the occasion of drops and charging at the same time by furnishing an electric field, which leads to the conformation of elongated result drops.

3.3.5. Microfluidic and Jet Dispensing Approaches

Microfluidics is an all-around technology which allows analyses to be conducted at really high output by streaming thousands of samples per second and controlling fluids in networks of micro meter- sized waterways. According to this stage, the soaked results of parent composites and co-formers were dissolved in colourful detergents at veritably small amounts for a single chip through combinatorial mixing. By applying a two- phase webbing process, caffeine was reused with a wide range of co-formers and colourful detergents to identify combinations with the up most tendency for cocrystals. The parent emulsion (caffeine) was introduced into the chips vertically, while the co-formers were introduced into the chips horizontally. The results proved that cocrystals screening using microfluidic chips is dependable and reproducible [7].

3.3.6. Spray drying

Spray drying is a continued single- step system of metamorphosis of liquids (results, dormancies, slurries) to solid powders. It is beneficial due to its continued, largely controllable, and fast process. Although spray drying has been extensively used in formulating unformed solid dissipations because of the fast solidification process, it has also been employed in conflation of co-crystal. Spot drying dried several combinations of API- co-former with the purpose of co-crystallization. They claim that co-crystallization has been observed in largely supersaturated regions of the medicine due to the rapid-fire detergent evaporation, presence of the co-former, or commerce between the medicine and co-former in liquid form. Another operation of spray drying to induce pharmaceutical cocrystals was done to prepare the carbamazepine − nicotinamide co-crystal (CNC; 11). Also, it was proved that TPD can be used for the conformation of co-crystals by industrially viable spray drying techniques [38].

Table 2. List of BCS II drugs along with their coformers and their method of preparation.

Drug	Coformer	Method of Preparation	References
Ibuprofen	Nicotinamide	Solvent evaporation method	[40]
Darunavir	Succinic acid	Cooling crystallization method	[41]
Atorvastatin calcium	Aspartame	Slurry conversion	[42]
Aceclofenac	Nicotinamide	Neat grinding	[43]
Gliclazide	Succinic acid and malic acid	Liquid-assisted grinding	[44]
Quercetin	Caffeine, nicotinamide	Electrospray technique	[45]

4. Applications of Co-Crystals

A various system to enhance the solubility and bioavailability of drugs that are inadequately water solvable is co-crystallization, particularly for substances that are neutral or weakly ionized in nature. also, co-crystallization offers the chance to change and enhance melting point, tablet capability, solubility, stability, bioavailability, and permeability. By modifying drug solubility, pharmacokinetics, and bioavailability, crystals have the capability to enhance the delivery and clinical efficacity of pharmaceutical products. Using co-crystals in particular to enhance the oral drug absorption of BCS class II and IV drugs. By applying the solvent volatilization process, flavonoids (naringenin and baccalein) were used to produce oxaliplatin co-crystals with the aim of enhancing GI tract solubility and stability while minimising adverse/ toxic effects. Furthermore, meloxicam pH-dependent solubility complicates the creation of novel oral formulations. Transdermal distribution of this drug has been proposed as a result to these limitations. The co-crystallization system can be utilised effectively to increase meloxicam cutaneous permeability by using salicylic acid as a conformer.[46] Nutraceuticals, which are having good health benefits can also be used as co-formers for better associated health benefits along with the API. By using the co-formers similar as saccharin sodium, the bitter taste of the API can be modified there by co-crystallization method can be used in case of fast dissolving tablets. Though there are plenitude of co-crystals available in the literature, some of the reported co-crystals are presented, based on the system of preparation.

Now multi-drug co-crystal (MDC) is also growing attraction among pharmaceutical scientists [47]. MDC have synergistic effects, increased solubility, bioavailability, and potential to stabilize unstable components via intermolecular reactions [48].

Future prospective

Co-crystals give an encouraging future in various fields, including pharmaceuticals and materials science. The synthesis and characterization of co-crystals bear specialized methods and expertise. Developing scalable and reproducible manufacturing procedures is essential for industrial operations [49]. In the near future, it is expected that the development of industrially relevant processes for co-crystal formation and the use of nutraceuticals as co-formers for the extra benefits will occur [50]. The co-crystallization method is most beneficial for some medications which undergo degradation because of some conditions similar as basic or acidic surroundings or deficient of basic or acidic group for the conformation of salt. Nowadays researchers are showing further interest towards co-crystals due its perfect advantages. It'll be nothing unanticipated if co-crystals become most significant in the pharmaceutical market [51].

CONCLUSIONS

Poor aqueous solubility is the main disadvantage in successful drug delivery through the oral route. Several studies have been done to improve the oral bioavailability of drugs. In the last few years, pharmaceutical cocrystal become the centre of attraction for scientist and pharmaceutical industries to enhance the solubility of low water-soluble drugs by modifying their unwanted physicochemical properties. Pharmaceutical cocrystal has been proven an extensively potential method for the enhancement of drug solubility, stability, and bioavailability. Still, there are several challenges including co former selection, physicochemical

characterization and expression. Careful drug conformer screening and expression design can lead to successful Cocrystals development. In this review, we discussed in detail a wide range of technologies applied for experimental screening, synthesis and manufacturing of pharmaceutical co-crystals in order to overcome poor physical properties of APIs. On early development, co-crystallization processes mainly focus on and detail discuss about common method of cocrystal preparation such as solution-based method, solid-based method and miscellaneous method.

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