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Co-Crystals for Improving Solubility and Bioavailability of Pharmaceutical Products

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Abstract

Poor drug solubility with the consequent low bioavailability represents one of the main obstacles to the introduction of new drugs into the market. Several approaches were tried to improve drugs poor solubility and low bioavailability, one of these feasible approaches is by using co-crystallization technology which depends on co-crystal formation by joining the drug with another active pharmaceutical former which could alter the parent drug physicochemical properties. This review tries to highlight the main points in co-crystallization technology including co-crystals design, methods of preparation, the different ways of characterizations and diverse co-crystal applications in product development. Co-crystal design could be facilitated by different software programs like Cambridge structure database, which may aid in prediction of the cocrystal production. Various techniques were used in preparation of co-crystal including classical methods (dry grinding, wet grinding and solvent evaporation) and green methods (ultrasonic and microwave-assisted techniques). The characterization of co-crystal is a corner stone in this field. The developed co-crystal could be identified by their structure, thermal behavior and morphology. Different aspects for co-crystal applications in improving solubility, stability, taste, bioavailability and formulation performance of solid dosage forms were discussed. Indeed, co-crystal could improve flowability and compressibility of powder and consequently will help in production of tablet dosage form. Moreover, multi-drugs co-crystals have succeeded in reaching the market with great advantages in reducing the required dose to perform the pharmacological action in a synergistic performance with another pharmacological agent.

Keywords: Bioavailability; Co-crystal; Coformer; solubility enhancemen.

1. Introduction

In drug industries, the discovery of new active pharmaceutical ingredient (API) is not the only problem that scientists face. However, the choice of the best form that ensures the delivery of the required dose to the site of action inside the body is another challenge. As most of the APIs are founded as solids, a compromise should be accomplished between physicochemical properties, solubility, stability and other formulation properties to give the best handling and bioavailability characteristics with the lowest possible cost. Co-crystal is a type of solid form of the drug that could be used to improve dissolution rate, stability, flowability, taste, and bioavailability [1].

Crystallization is a process of repetitive organized arrangement of the molecules to form a single crystal [2]. Co-crystal is a type of solid crystal that formed when the stoichiometric ratio of correlative atoms of various structures is solidified to one crystal and when this co-crystal dissolves it will give back its original starting material. It is like a physical bond that brings different compounds together [3]. The United States Food and Drug Administration (FDA) defines co-crystals in the draft guidance as: “Solids that are crystalline materials composed of two or more molecules in the same crystal lattice” [4], [5]. This definition has limitations as it considers the co-crystal could be formed only from molecules, but scientific researches approved that it could contain ionic components as well [5]. So, it is better to define co-crystal as single phase crystal solids consist of two or more different components which are either molecular or ionic compounds usually in a 1:1 ratio and joined together by non-covalent bonds (mostly hydrogen bonds) [1], [5]. Other types of bonds that may involve in co-crystal formations include van der Waals forces, halogen bonding, and π–π interactions [6].

In 1844 Friedrich Wöhler discovered quinhydrone co-crystal during his study on quinone [7]. But this co-crystal was not fully prescribed and analyzed as

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X-ray diffraction apparatus was not discovered at that time. Quinhydrone co-crystal intermolecular bonds and full structure was reported in 1958. It is consisted of a similar ratio (1:1) of quinone and hydroquinone [8] as illustrated in Figure 1.

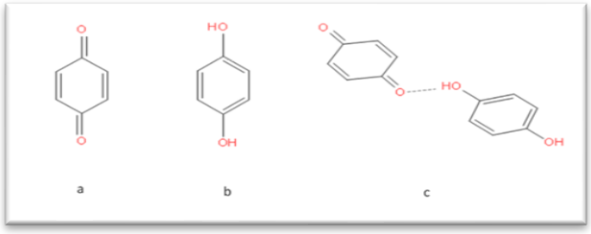

Fig 1. Structures of: (a) quinone, (b) hydroquinone, and (c) quinhydrone co-crystal.

Pharmaceutical co-crystals could be classified according to the therapeutic activity of their components into:

1. Single drug co-crystals: These co-crystals contain APIs and excipients (co-crystal former) which is called (coformer). Pharmaceutical coformers are selected from lists provided by the FDA, these lists contain the names of all materials which are considered as safe to use in drug and food industry and they are known by the term generally regarded as safe (GRAS) [9]. Coformers are mostly water soluble molecules used to change and improve the physicochemical properties of the APIs, for example caffeine, nicotinamide, saccharine, oxalic, malonic, succinic, ascorbic and carboxylic acids [10]–[12]. The poor water solubility of the antiepileptic drug, carbamazepine, has been improved when it is formulated as a co-crystal with saccharine coformer [13].

2. Multidrug co-crystals: which consist of two or more APIs usually in a stoichiometric ratio. This type of solid single phase multi-components system offers not only synergistic effects due to the presence of two drugs in the same crystal lattice, but may improve solubility, dissolution rate, and bioavailability of at least one of these two APIs molecule [14]. FDA approved Entresto™ tablet in 2015 for heart failure treatment, it consists of multidrug co-crystal which are an angiotensin II receptor blocker (valsartan) and neprilysin inhibitor (sacubitril). This co-crystal gives clear evidence about how co-crystal can cause changes in pharmacokinetic properties, leading to improve bioavailability and give the same drug activity at lower doses [15], [16].

Indeed, there is an overlapping between co-crystal and other solid multi-component forms like salt, solvate, and hydrate (Figure 2). In the case of salt, there is a proton transfer leading to cation/anion (ionizable group) formation rather than proton sharing due to hydrogen bonding which is found in co-crystal and this depend on the pKa differences. In most cases of co-crystal, the difference in pKa is less than 1, although pKa difference as great as 4 has been reported [17]–[19].

Solvate and hydrate are solid-phase crystals. They are different from co-crystal because all components of co-crystal are solids at room temperature, while in solvate\hydrate one of the constituents is liquid (water in hydrate) at ambient condition, that is to say, the coformer in solvate or hydrate is in a liquid state [20], [21].

Although, some of the preparation methods of solid dispersion and co-crystal have similar process steps. But there are huge differences between co-crystal and solid dispersion. In co-crystal, the API binds with co-former by non-covalent bonds while in solid dispersion the hydrophobic API disperses in hydrophilic carrier like: crystalline carrier, amorphous polymeric carrier and surfactant. Also solid dispersion is considered to be unstable (thermodynamically) and shows changes in crystallinity. while this is the opposite to co-crystal which is known by its high stability [22].

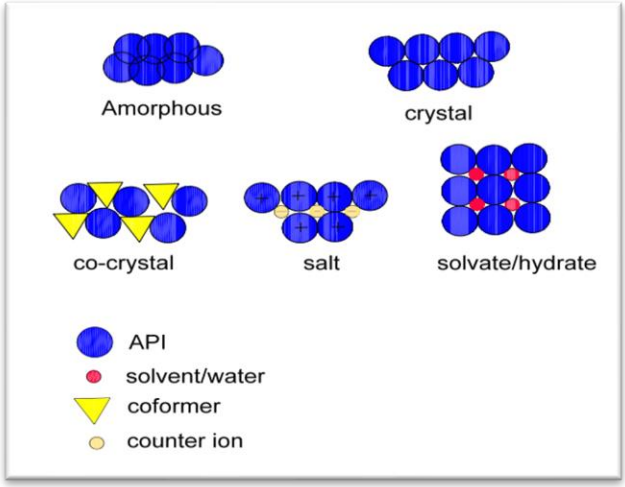

Fig 2. Different possible solid-state pharmaceutical multicomponent systems.

2. Co-crystal design

There is a diversity in solid APIs and coformers, but not all of them are good candidates for co-crystals manufacture. There are some theoretical, experimental and computational data-based program methods which that can help researchers in the prediction of co-crystal creation from the selected or available APIs and/or coformers [23]. The most common methods are:

2.1. Hydrogen bonding

Co-crystal creation depends on the non-covalent interactions between their different constituents; in most cases, the type of non-covalent interactions are hydrogen bonds. The formation of hydrogen bond

(HB) depends on the presence of HB donor and HB acceptor. The HB donor is the group that can give hydrogen, like phenolic O−H, carboxylic O-H, and amine N−H. And the HB acceptor is the group that can accept hydrogen like the amidic N− C=O and a carboxylic C=O oxygen atom. The presence of these HB donors and acceptors as a functional group in the APIs and coformers will help in predicting the co-crystal formation [23], [24]. In 1991 Etter and his colleague set 3 general standards for HB formation, which are [25]:

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six membered rings intramolecular HBs form in preference to intermolecular HBs.
3. The best proton donor, and acceptor remaining after intramolecular HB formation will form intermolecular HBs to one another (however, it is not necessary that all acceptors will bind to donors groups).

Following the above rules will aid in finding a theoretical way to forecast co-crystal formation depending on molecular interaction between functional groups of APIs and/or coformers [26].

2.2. Cambridge structural database (CSD)

It is like a data store that contains complete files of all distributed crystal small-molecules with their three-dimensional structure. It is available as a software used by students or researchers, and undergo annual updating [27].

CSD is a useful tool for screening co-crystal components; it provides better understanding of intermolecular arrangements, hydrogen bonding and the best fitting between APIs and coformers. CSD depending programs could save time and money through a selection of the best complementary candidate from several components having the required functional group to give the intended co-crystal [26], [28], [29].

3. Co-crystal preparation methods

Various methods used in the production of co-crystals, they range from simple neat grinding to more complicated gas anti-solvent co-crystallization. According to the amount of solvent used, the preparation methods can be divided into solid-state and solvent-based co-crystallization [30].

3.1. Solid-state methods

In these methods, nil to a very little amount of solvent is used in the synthesis of co-crystals and for this reason, they can be subdivided into neat dry grinding and liquid-assisted grinding.

3.1.1. Neat (dry) grinding

In this type of grinding, co-crystal formation depends on mixing while applying pressure to a solid mixture of APIs and coformers. The mixing is either manually by mortar and pestle or mechanically by vibratory or ball milling. The temperature and time of mixing are controlled to give the best product, the common grinding duration ranges from 30 to 60 minutes [30].

The advantage of this method is that it eliminates the need for solvent use, so no stability problem will occur, the main flaw is the low efficacy of co-crystal formation due to dry mixing some of the product will convert to amorphous form, and the resultant sample will be impure and need further purification [30], [31].

3.1.2. Wet (Liquid-assisted) grinding

A catalytic amount of liquid is added to solid powders before milling, different solvents could be used in this method like water, ethanol, toluene and many others. Only a few microliters or drops of solvent are needed. This method, also called solvent drop grinding, increases co-crystal formation as the liquid acts as a binder, to bind solid powders, rather than dissolution media [30]–[32].

The advantages of this method are simple, effective, green, low cost and give co-crystal with higher purity than other methods. Also, this method increases yield percentage in comparison to dry grinding [31], [33].

3.2. Solvent- based methods:

These methods are more frequently used procedures; they depend on the addition of a large amount of solvent in which both APIs and coformers should be dissolved. The crucial step in this method is the solvent selection process. Changing the solvent and/or temperature to give the best co-crystal characteristics [34]. In solvent dependent co-crystallization method, the crystallization of compound out of solution occurs when the solvent becomes supersaturated with co-crystal. Thus the rate limited step in solvent-based method is when the degree of solvent unsaturation is lower than the co-crystallization rate [35].

Many methods are classified as solvent-based such as solvent evaporation, slurring, active co-crystallization and anti-solvent method, but the most important one is solvent evaporation method [34].

3.2.1. Solvent evaporation method

It is one of the most common methods for co-crystal preparation, it consists of dissolving equimolar amount of API and coformer in solvent or mixture of solvents. The solvent facilitates molecular interaction and bond formation, after that the evaporation will reveal the formed co-crystal. The rate of evaporation should be monitored carefully; rapid evaporation rate usually gives large number of small co-crystal while slow evaporation rate gives

few number of large co-crystal. Evaporation of the solvent occurs either spontaneously at room temperature or by using accelerated techniques which depend on increase temperature and\or decrease pressure such as rotatory evaporator and vacuum filtration [30], [36], [37].

3.3. Green techniques for production of co-crystals

These are new types of techniques that focus on designing products and processes that decrease or eliminate the need and production of hazardous substances such as eliminating the use of organic solvent [38].

3.3.1. Ultrasound assisted co-crystallization

This is a new method involves ultrasound waves; these waves facilitate phase transformation processes leading to co-crystal production in a short time as it induces nucleation in solution [39], [40].

Ultrasound apparatus or sonicator found in two forms ultrasonic probe and ultrasonic bath.

• **Ultrasonic probe** consists of a solid probe and sono-reactor vessel with a temperature controller. Aher *et al* tried to prepare different molar ratios of caffeine: maleic acid co-crystal using the ultrasonic probe, the probe operates at constant vibration equal to 20 kHz. Caffeine and maleic acid feed into the vessel in the form of solution or slurry with methanol as a solvent, then the ultrasonic probe plays in a cycle of alternative ultrasound pulses (10 sec) with relaxation time (2 sec). Circulation of cold water from a water bath through a glass jacket may need to avoid excess heating. The resultant product was filtrated to give the required co-crystal. A co-crystal of caffeine\ maleic acid in two to one (2:1) ratio is prepared by using this method [41].

• **Ultrasonic bath** is a vibration generating water bath. The powders will be dissolved in the solvent in a glass vial which will be sonicated at a controlled temperature until clear solution is obtained, after that the sonicater will turn off and the solution will be filtrated to reveal the co-crystal [42]. Rodrigues *et al* formed hydrochlorothiazide co-crystals with different coformers by using ultrasonic bath, the physical mixture of API and co-former distributed in solvent, sonicated in ultra-sonic bath for 4 hours, at 40 °C. after that the solvent left to evaporate at room temperature and the co-crystals harvested for further characterization [43].

3.3.2. Microwave assisted co-crystallization:

Microwave radiations cause excitation and increase molecular mobility by the interaction between these radiations and the rotating dipoles of the molecule which will lead to rapid co-crystallization as the radiation heat maintain supersaturated solvent and ensure its evaporation in short time [44]. Microwaves generating sources that can be used in co-crystallization are either: a domestic microwave or a microwave reactor like (Monowave 300, Anton Paar GmbH, Austria). Microwave reactor differs from the domestic one as both the power and pressure produced by the reactor could be controlled precisely [45], [46].

The APIs and coformer powders will be dissolved in a suitable solvent depending on dielectric properties and solubility profiles, then the sample will transfer to glass tubes, and set the microwave to the required temperature, time and power. At the end, the solution is filtered to give co-crystal [44].

4. Co-crystal characterization methods

The methods used for co-crystal characterization could be classified as in Table 1 into various classes: Co-crystal structure determination, thermal analysis and, morphology determination.

Co-crystal structure determination could be performed by different methods like X-ray diffraction, Raman spectroscopy and, Fourier-Transform Infrared (FTIR) spectroscopy. However, X-ray diffraction (single crystal or powder) gives a definite diagnosis about the formation of new co-crystal when there are changes in the X-ray pattern from the original material pattern. Raman spectroscopy is a useful technique for co-crystal diagnosis, changes in the vibrational mode of the material due to light scattering may indicate co-crystal formation as well [47].

FTIR represents the fingerprint of each compound, the functional group represented by peaks in a certain range area, whenever there is a new band, or shifting in an already existing peaks, this may indicate hydrogen bond formation and further investigation is needed to ensure co-crystal formation. FTIR is useful tool in the selection of suitable co-former from series of compounds in co-crystal construction [48], [49].

Thermal analysis approach depends on the variation in melting points and enthalpy among the co-crystal, its components (APIs and coformer) and their physical mixture. The thermal analysis includes differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA) [50].

In DSC; the formation of the endothermic peak at lower or in between the melting points of the raw materials, indicates co-crystal formation. DSC technique relies on measurement of phase changes such as melting, polymorphism and losing of the co-crystal volatile component.

DSC detects the power changes as a function of temperature, while TGA records the loss in mass as a function of temperature. TGA considered as a good method to detect the exact temperature at which the co-crystal starts to decompose and loss its volatile component. The quantity of mass loss in TGA

provides confirmed information about the stoichiometric ratio of co-crystal starting materials [48], [51].

Table 1: Co-crystal characterization methods.

Characterization principle	Diagnosis methods
Structural and spectroscopy	Single crystal X-ray diffraction. SCXD.
	Powder X-ray diffraction. PRXD.
	Fourier-Transform Infrared FTIR spectroscopy.
	Nuclear magnetic resonance NMR spectroscopy.
	Raman spectroscopy.
Thermal	Melting point.
	Differential scanning calorimetry (DSC).
	Thermo gravimetric analysis (TGA).
	Hot-Stage Microscopy (HSM) or Kofler method*.
Morphological	Polarized optical microscopy.
	Fluorescence microscopy.
	Scanning Electron Microscopy (SEM).

*Thermal microscopic method.

Morphological study ranges from using an optical microscope to scanning electron microscope (SEM). SEM consists of a beam of electrons that focused on the surface of the scanned particles to gives a three dimensional image, clarify the morphological shape like (cubic, round or needle) and surface characteristics such as (smooth or rough) [40], [50], [52].

5. Pharmaceutical Co-crystal applications

The formulation of a new co-crystal based on its original API and coformer will completely affected its physical and chemical properties, and this will give a total deviation in formulation and manufacturing process leading to a more effective dosage form [30]. Co-crystal pharmaceutical applications are summarized in Table 2.

5.1. Changing physicochemical properties

the co-crystal will adjust the original drug physical and chemical characteristics. This results from thermal changes in co-crystal because of its distinct melting point. The co-crystal is used to improve solubility, dissolution, stability, and bioavailability [53].

5.1.1. Improving solubility, dissolution and bioavailability

The classification of drugs into four classes by Bio-pharmaceutics Classification System (BCS), according to its solubility and permeability, revealed that about 40% of the marketed drugs have poor solubility. Researchers focused on improving solubility of such drugs by different techniques including the uses of co-crystal formulation [54].

Shimpi *et al* formulated a co-crystal of Tadalafil (phosphodiesterase inhibitor) with-malonic acid. This co-crystal had 100 times higher aqueous solubility over a wide range of pH when compared to the drug alone. Eutectic mixture of Tadalfil with coformer found to have 1.1 to 1.5 folds increase in solubility in compare to the pure tadafil [55] .

A new inhibitor of blood coagulation, Apixaban drug is successfully prepared by Chen *et al* as co-crystal with oxalic acid. They approved that this co-crystal improved solubility and intrinsic dissolution rate in buffer solution (pH 6.8) by 2.2 and 2.1 times than apixaban forms. Also, they conducted a pharmacokinetic study in Beagle dogs and measured the area under the curve (AUC) and the plasma concentration. AUC is higher in co-crystal than free apixaban by 2.7 fold. The enhancements that occurred in solubility and bioavailability with reasonable stability suggested a new form of apixaban that could be used very effectively in drug formulation [56].

A class II low water-soluble, sodium channel blocker API, pyrimidine-4-carboxamide derivative is formulated by McNamara *et al* as a co-crystal with Glutaric acid. This study approved that using water soluble co-former (glutaric acid) in co-crystal formation could improve solubility and intrinsic dissolution rate by 18 fold and this is reflected *in vivo* plasma concentration measurement in dogs which has been increased by approximately 3 times in comparison to the free API [57].

Sugandha and his colleague, illustrate how the use of Ezetimibe, antihyperlipidemic agent, as co-crystal with methyl paraben could improve solubility and dissolution. They prepared ezetimibe co-crystals by three different methods: liquid-assisted grinding, solution crystallization, and reaction crystallization. All three co-crystals showed higher solubility (approximately 2- fold) than free ezetimibe, besides the improvement that occurs to dissolution and bioavailability making these co-crystals a good alternative to ezetimibe in the drug industry [58].

Piperine a plant-derived secondary metabolite has several pharmaceutical applications in pain, inflammation, and gastrointestinal dysfunctions, but it uses is limited by its poor solubility, dissolution and bioavailability. To solve all of these problems, Zaini and his colleague formulated piperine as a co-

crystal with succinic acid coformer. This novel co-crystal showed a four-fold increase in solubility in comparison to piperine alone. Dissolution and bioavailability have been improved also. The mechanism of solubility enhancement has been attributed to the formation of channels between the piperine molecules due to the rapid dissolution of water soluble co-former succinic acid [59].

5.1.2. Enhancement of drug stability

Formulation of some drugs as co-crystal showed a good enhancement in stability such as formulation of non-steroidal anti-inflammatory drug flufenamic acid as co-crystals with two different drugs (nitrobenzoic acid and ethenzamide) by formation of weak halogen bond that stabilize the flufenamic over 6 months at ambient condition [51].

Berberine, isoquinoline alkaloid natural extract with multiple pharmacological activities is prepared with Fumaric acid as co-crystal by Yang *et al*, it showed an improvement in solubility in addition to its stability at higher temperature and humidity. The stability study was performed by measuring stress and Dynamic Vapour Sorption (DVS) [60].

5.2. Improving mechanical properties of tablet

Tablet production is challenged by two variables: compressibility and flowability which are affected by the physicochemical properties of the API, mainly the particle size and shape. Compressibility is the most important mechanical property that could be altered by co-crystal formation.

A dramatically enhancement in compression properties of caffeine tablet was achieved by formulating caffeine as a co-crystal with methyl gallate. Powder compaction was studied closely along with tableting characteristics of co-crystal including weight, dimensions, and tensile strength which is found to be 2 times higher than tensile strength of caffeine alone [61].

A new compressible form of paracetamol tablet is formulated by Karki and his colleagues, using co-crystal engineering technique of paracetamol with four different co-formers (oxalic acid, naphthalene, theophylline and phenazine). They measured the tensile strengths and other mechanical parameters like (tablets diameter, thickness and hardness) of the four paracetamol co-crystal tablets, comparing them with each other. In spite of the inability to formulate paracetamol alone as tablet by direct compression; paracetamol co-crystals formulated easily with good hardness; the forces that required for breaking co-crystal tablets were between 40 to 52 Newton. The tensile strength was highest for paracetamol/ theophylline and lowest for paracetamol/oxalic acid co-crystal tablets [12].

Table 2: Co-crystal applications [30], [33].

Pharmaceutical co-crystals are used to:
Increase solubility.
Enhance stability.
Improvement in dissolution rate.
Improve absorption and pharmacokinetic properties.
Enhance drug bioavailability.
Improve compression and flowability.
Masking bitter taste.
Formulate a control release dosage form.
Better purification and separation of the APIs.
Formulate drug- drug co-crystal.
Formulate nutraceutical co-crystals.
Formulate Nano-co-crystals.
Pharmaceutical intellectual property extension.

5.3. Improving organoleptic properties, palatability

improving the taste of oral dosage form is an important aspect in drug formulation. In co-crystallization, the use of artificial sweetener as a co-former may exhibit a dual action as they mask the bitter taste of APIs in addition to their effect in co-crystallization. One of the most important artificial sweeteners, used as co-former is saccharine [30].

Preparation of paracetamol co-crystal with trimethylglycine by Maeno *et al*, showed a good masking of the bitter taste of paracetamol beside the improvement that occurs in the compression, tableting and dissolution properties [62].

5.4. Multidrug co-crystals

Combination of two drugs in one formulation offers several advantages. In addition to the synergistic effect of multi drugs co-crystal, improvement in physicochemical properties of at least one drug could obtain as well. Drug-Drug co-crystal is an important formulation aspect in case of multi drug regime system such antituberculosis treatments, analgesics, anti-inflammatory, antiviral and diuretics drugs [14], [16].

For example, tramadol-paracetamol co-crystal provides a pain relief effect with a lower dose of tramadol. Buschmann *et al* claim that this co-crystal could improve solubility, decrease hygroscopicity, enhance efficacy-dose response and bioavailability [63].

Non-steroidal anti-inflammatory drugs (meloxicam and aspirin) co-crystal which has been prepared by different methods showed an improvement in solubility and pharmacokinetics properties. The solubility in phosphate buffer at

intestinal pH 7.4 increase from 0.005 mg/ml (for meloxicam alone) to 0.22mg/ml (for meloxicam co-crystal). Pharmacokinetics study of this co-crystal in rats revealed an improvement in oral bioavailability (69%) when compared to meloxicam alone (16%). The maximum concentration (C_{max}) is four time greater in meloxicam co-crystal with twelve fold decrease in the time required to reach an optimum concentration in comparison to meloxicam alone [64].

Two antibacterial drugs (Nitrofurantoin and Trimethoprim) that used for treatment of urinary tract infection showed a higher solubility and better activity against certain bacterial strain when formulated in form of co-crystal. This co-crystal showed a lower MIC (minimum inhibitory concentration) and higher antibacterial activity against *E.coli* gram-negative bacteria when compared with nitrofurantoin and trimethoprim alone [65].

6. Conclusions

Recently, a new pharmaceutical trend was used to design a multicomponent formula like co-crystals which has been grown out to be an interesting technique in pharmaceutical industry. Different methods could be used very successfully in production of co-crystal including green techniques. However, recent including of new technique such as the hot melt extrusion and spray drying will be very useful in accelerating the co-crystal technology. Co-crystals technology has been used successfully in diverse applications in pharmaceutics and drug delivery. Co-crystals proved to change the physicochemical properties that enhance the formulation achievement through modification of key formulation characteristics like powder flowability and compression ability. In addition, co-crystal is a useful tool in formulating drugs with low solubility like class II drugs or even improving solubility and permeability as in case of class IV drugs. In addition to the formulation improvement, co-crystal improves the pharmacokinetics, stability and bioavailability performance. Multi drugs co-crystal represent a unique formulation that offers dual, triple or even multi benefits over the original drugs. Multi drugs co-crystal gives a synergistic effect at lower doses, with reduced side effect, improved bioavailability and with consequent improved clinical effect. All these together will encourage the researchers for more interest in co-crystal in near future and we hope this review will help in introducing this technology to the whole community in pharmaceutical sciences.

7. Conflicts of interest

"There are no conflicts to declare".

8. Formatting of funding sources

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