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CO-CRYSTALLIZATION: A NOVEL APPROACH TO ENHANCE THE DISSOLUTION OF POORLY SOLUBLE DRUGS

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ABSTRACT

Approximately 40% of newly synthesized drugs are not able to enter market due to biopharmaceutical issues like poor solubility and poor permeability. Most number of drugs marketed is administered orally hence solubility enhancement plays a major role. There are different techniques to upgrade the dissolvability of inefficiently soluble drugs including pro-drug approach, salt formation, particle size reduction, complexation and solid dispersion. Out of all other techniques, salt formation is one of majorly used technique to improve physicochemical characteristics of drugs which includes formation of ionic bond. But nowadays development of co-crystals has evolved as a suitable technique towards improving the dissolvability and bioavailability of ineffectively soluble drugs that includes non-ionic bond formation. In this paper a brief and accurate precis of pharmaceutical co-crystals is stated with specific spotlight on co-crystal preparation methodologies, mechanism of co-crystal formation, characterization methods and some of the examples of pharmaceutical co-crystals are additionally outlined. The difference between salts and co-crystals, regulatory facet and also the future prospective of co-crystallization is being discussed.

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INTRODUCTION

Drug substances having low aqueous solubility are becoming extensively widespread in the research and development speculations of discovery oriented pharmaceutical companies [1]. The most recent decade has seen a substantial number of new chemical entities coming into poorly soluble drug category which commonly leads to poor oral bioavailability [2]. According to biopharmaceutical classification system the drugs get classified into four major categories depending upon their solubility and permeability BCS Class 2 and class 4 drugs majorly suffer from low aqueous solubility leading to poor absorption and bioavailability which faces challenges for drug development process. Upgrading bioavailability of inadequately water-solvent BCS class 2 and BCS class 4 drugs finds most important to improve efficacy of drugs [3]. Approximately 70-90% of newly synthesized molecules are belonging to BCS class 2 and 4 compounds [5].

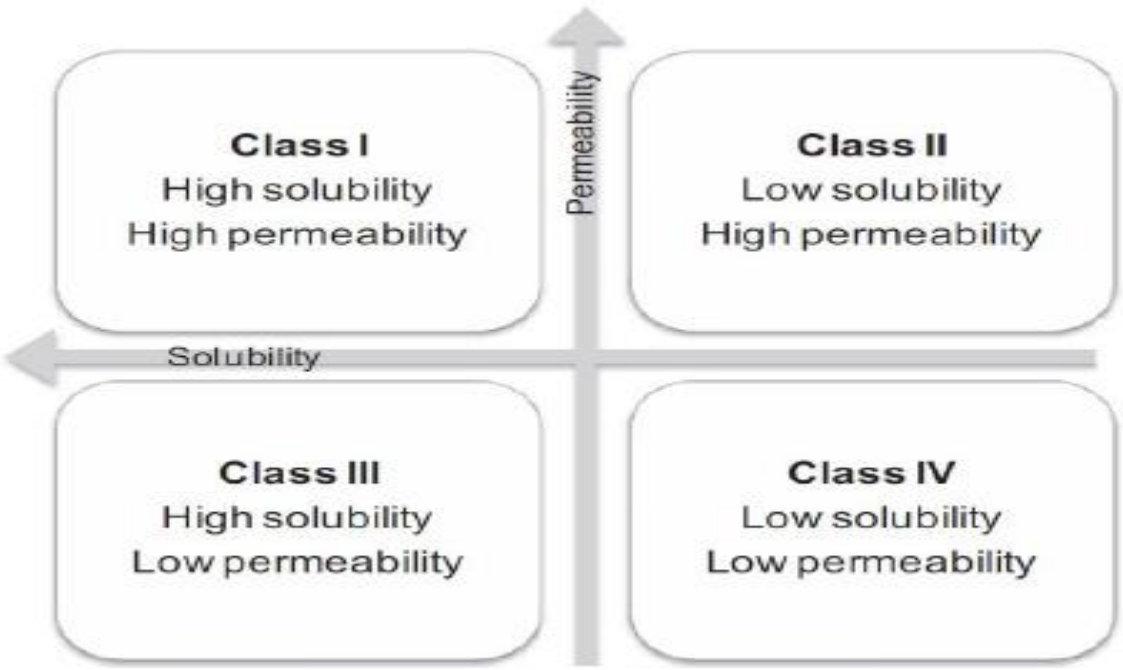

Figure 1: Schematic representation of Biopharmaceutical classification system of drugs [21].

Improving the dissolvability of medication is right now one of the primary difficulties for pharmaceutical industries [6]. Pharmaceutical company engaged with formulation development are confronting tremendous issue while managing unwanted execution qualities of drugs. Unluckily numerous drugs with generally excellent pharmacological action will show ominous bioavailability because of unwanted physical properties [7]. On the off chance that a medication cannot break down in the gastro-intestinal tract or enter tissue, at that point it will experience issues discovering therapeutic use [15]. In the course of most recent decade, there has been developing interests in the plan of pharmaceutical co-crystal, which rises as a potential technique for increasing the bioavailability of drugs with low aqueous solubility. Some of the techniques have been adopted for enhancing the aqueous solubility of medication including micronization, salt formation, emulsification and solubilisation using co-solvents, solvates and polymorphs etc [6]. Alongside these accessible methodologies to improve the bioavailability of medications, formation of co-crystals of an active pharmaceutical ingredient (API) opened another road as an alternative methodology [7]. In case of neutral compounds or weakly ionisable compounds, the co-crystallization plays a better role than any other technique in terms of enhancement of solubility of a drug as it includes non-ionic interaction [29]. The advancement of first co-crystal can be followed in 1844, when Wohler synthesised quinhydrone complex which was later observed to be 1:1 co-crystal of quinine and hydroquinone [21, 16, 2]. Actually, a large number of the first co-crystals were covered up under various names, for example, adducts, molecular complexes, organic molecular compounds and solid state complexes. Many were found in the mid 1990s [30]. In 1995, desiraju initiated the idea of the supramolecular synthon or hydrogen bonded building units in crystal structure. This idea promoted a spurt of research that was in charge of the board development in the field of co-crystals [2]. In case of ionisable drugs, the formation of salts is the easy and cost effective technique to overcome poor aqueous solubility to increase bioavailability, where in case of non-ionisable drugs having low pKa value in the scale where possible salt formation is very low, co-crystallization is an appealing/irresistible choice [18]. Co-crystal advancement is especially appealing when salt arrangement is infeasible or while existing Salts neglect to display appropriate properties for use in a drug product. Likewise, co-crystals of pharmaceutical salts, to be specific Ionic Co-crystals, may likewise be prepared and evaluated [24]. Extensively co-crystals can be characterized as crystalline materials comprise of at least two unique parts (or usually called multi-component crystal). In the pharmaceutical co-crystals, one part is an API and other part is called as crystals former or co-formers. Co-crystals have increased significant enthusiasm for pharmaceutical research because of its capacity to improve physicochemical attributes of an API. A few papers have been distributed in the ongoing past which gives a diagram of co-crystals [23].

There are wide varieties of advantages of co-crystallization such as enhancement of dissolvability, dissolution rate, bioavailability, extemporize physical, chemical stability and also mechanical properties [28]. Co-crystallization may either upgrade or lessen solubility or dissolution rate of a weekly soluble APIs. If we take an example, co-crystallization with benzoic acid lessens the dissolvability of fluoxetine hydrochloride yet succinic acid and fumaric acid co-crystals display improved solubility [20].

Some of the disadvantages of co-crystal are the uptake of moisture that could make a hydrated type or new polymorphic types of drug which may possibly influence the nature of the drug. The hydrolysis of certain drugs can occur because of moisture can influence on drug release pattern from formulation, shelf life, handling and transportation of formulation. Chemical stability of the compound can also be altered by molecular rearrangement in the crystal lattice due to co-crystallization [23]. The capacity of co-crystals to address physical stability issues of APIs, for example hydrate arrangement on introduction to high Relative Humidity (RH), is one of the most punctual exhibited favourable circumstances of co-crystallization. The chemical stability of drug substance may not be same as co-crystals simply because of the distinctive spatial arrangements of responding functional groups in the crystals. The distinctive melting point of the co-crystal (either lower or higher) and co-formers may likewise add to various stability behaviours at raised temperatures [20]. The mechanical properties of API are getting affected by large scale manufacturing for example during compaction and milling. Lacking mechanical properties regularly lead to issues in tablet formulation and manufacturing. Usually tensile strength of tablet is monitored by bond area and bonding strength between particles. If crystals have low plasticity then it leads to poor tabletability due to tiny bonding area occurred by compaction. In the mean time the high plasticity also leads to lower bond strength thus lead to poor tabletability. Hence the impacts of co-crystallization on tableting execution rely upon the relative crystal plasticity and bonding strength between the co-formers and the co-crystal [20].

Multi-drug combination offers an advantageous route for combination therapy and intellectual property opportunities. Albeit restorative efficacies of the two medications have been exclusively illustrated, an item utilizing the new strong structure between two medications still should be thoroughly tested to safety, bioavailability, strength and manufacturability. Other than marketed drugs, compounds showing pharmacological effects sold as nutraceuticals have been explored for co-crystal arrangement with both basic co-formers and marketed drugs [20]. Co-crystallization using solvent evaporation method is reported by Magdy M. Abdelquader *et al.* using olmesartan medoxomil and hydrochlorothiazide to prepare co-crystals which have shown increased solubility and dissolution rate. It is a fixed dose multi-drug combination used in treatment of hypertension [35]. The solubility and dissolution rate has been enhanced via co-crystallization is reported by Valerio Todaro *et al* where Caffeine is used as co-former with dapsone using Liquid assisted grinding methodology [33]. Recently Nilgun Sen prepared co-crystals of trinitrotoluene and 2, 6-diaminotoluene using solvent evaporation technique which is resulted in increased solubility [34]. Tatiane Cogo Machado *et al* has prepared co-crystals of meloxicam-salicylic acid as API and co-former via Reaction crystallization method. It is a novel approach that enhanced the transdermal administration of drug meloxicam [36]. Jian-Rong Wang *et al* has reported co-crystals of 6-mercaptopurine using isonicotinamide as co-former from reaction crystallization method have enhanced the dissolution rate of the drug [48]. Anindita Sarkar *et al* has reported co-crystals of acyclovir by using three different co-formers such as fumari acid, malonic acid and tartaric acid via both solvent evaporation and grinding technique has significantly altered the physicochemical properties such as solubility and dissolution rate. The co-crystals have shown greater solubility and dissolution rate compared to hydrated acyclovir [52].

The major goal of this article is to furnish a comprehensive idea on pharmaceutical co-crystals, its preparation methods, regulatory facet and future prospective. It is expected that this review article will give coherent information on co-crystals and stand as a starting step for further advancement of co-crystals.

Pharmaceutical co-crystal:

The definition of co-crystal is subjected to extensive debate at both chemical and legal level. The most general definition states that "co-crystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in stoichiometric ratios" [16]. As per Food and Drug Administration (FDA), co-crystals are defined as dissociable multi-component solid crystalline supramolecular complexes composed of two or more components within the same crystal lattice where in the components are in neutral state and interact via non-ionic interaction [21, 2]. As per Europe Medical Agency (EMA), co-crystals are homogenous crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangements in the crystal lattice are not based on ionic bonds. Co-crystal structure is majorly dependent on non-ionic interactions between the co-formers and API. The interactions involved are intermolecular interactions, such as hydrogen bonding, pi stacking, van der waals force, electrostatic interactions between stoichiometric amounts of various molecules [7]. The co-formers which are used in formation of co-crystals should not be toxic and should not posses any adverse reactions and it must be present on the United States Food and Drug Administration's (USFDA) Everything Added to Foods in United States (EAFUS) list and Generally Recognized As Safe (GRAS) list [9, 16, 8]. In order to prepare co-crystals, the API and co-formers should contain suitable functional groups which have the capacity of forming either homo or hetero supramolecular synthon. The bond that has formed in between API and co-former is non-covalent bond and crystal lattice is formed repetitively [9]. Drug-neutraceuticals coalescence could be supremacy and moderately more straightforwardness to create. Most neutraceuticals are weekly ionizing components that show poor bio-availability. Neutraceuticals based therapeutics, for example, apigenin, berberine, carnosic acid, ellagic acid, lipoic acid, curcumin and so forth, could offer potential stages for structuring therapeutic half and halves alongside API [21].

Selection of appropriate co-formers:

The co-former can be anything like amino-acid, vitamin, excipient, preservative, minerals and other API too [9]. Sometimes co-formers can be neutraceuticals which will have additional benefitial along with API [21]. One of the main challenges in pharmaceutical co-crystal development is the selection of co-formers that are compatible with a particular API [19].

The three major parameters to choose suitable co-formers are:-

a) Supramolecular synthon approach
b) Hansen solubility parameter
c) Cambridge structural database [19]

Supramolecular synthon approach:

In supramolecular synthons approach, steps engaged with creating co-crystals are as per the following:-

✓ Selection of target API.
✓ Selecting the complementary functional groups which are capable of forming a hydrogen bond. (co-former selection)
✓ Screening of co-crystals.

One of the primary difficulties in pharmaceutical co-crystal improvement is the determination of co-formers that are compatible with specific API. The term synthon was authored by Corey with regards to organic chemistry and characterized as "Structural units within supermolecules which can be formed and/or assembled by known or conceivable inter-molecular interactions" [19]. The formation of synthon is governed by the strength of hydrogen bond between the co-former and API [4]. The supramolecular synthon approach is very helpful in foreseeing the probability of co-crystal development over contending self-arranging of the two parts. This approach searches for oftentimes happening and thus reproducible patterns of intermolecular interactions to identify suitable forms that can be utilized to design a co-crystal structure. Such interactions might be effectively perceived like the well-characterized carboxylic acid dimer or Amide NH•••O hydrogen bonding themes or they might be Interactions for example π-Stacking, interactions between aliphatic chains or halogen bonding themes [26]. Usually the functional groups such as amides, alcohols and carboxylic acids tend to form non-ionic bond by interacting with one another to form co-crystals [22]. Recently Ling Ling Zheng *et al* synthesized two supramolecular assemblies of basic benzoguanamine and flexible cyclohexanedicarboxylic acids via solvent evaporation method [37].

The Supramolecular synthons are further categorized into: - [19]

I. **Supramolecular Homosynthon:** composed of identical self-complementary functionalities.
II. **Supramolecular Heterosynthons:** composed of different but complementary functionalities.

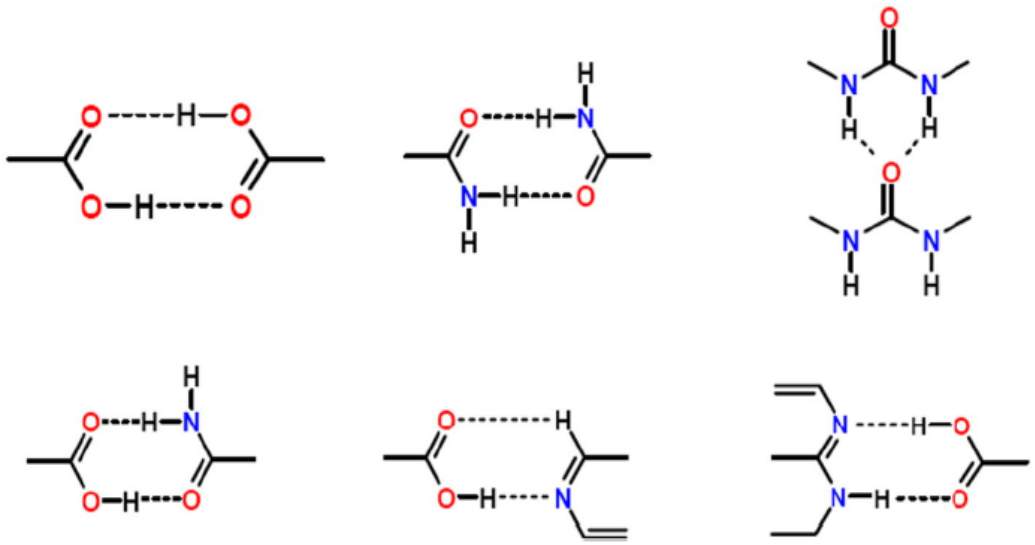

Figure 2: Common supramolecular synthons formed from carboxylic acids, amides, pyridines and other aromatic nitrogens [25].

Hansen solubility parameter:

Hansen solubility parameters (HSPs) set up in 1967 by Charles M. Hansen speaks to a stage forward from the Hildebrand solubility parameter. HSP is a methodology where the fluids absolute cohesion vitality is part into commitments from atomic dispersion, dipole-dipole/polar interactions and hydrogen bonding. The commitment in the HSP is separated into hydrogen-bond donor and acceptor values. For a given fluid pair, the closer are the HSP values in the three dimensional HSP space, the more prominent is their likeness, and subsequently their fondness is more grounded. This investigation is especially helpful in polymer dissolution. The idea has been extended from polymer blending to blending of a wide scope of materials including Pharmaceutical co-crystals [27]. Co-crystals are miscible frameworks at an atomic dimension. It is in this manner guessed that a marker of the miscibility of the part atoms in the strong state could foresee the probability of co-crystal formation [19]. The major benefit of HSPs is that it is a straightforward hypothetical methodology, requiring knowledge of molecules chemical structure as it were. It has even been depicted as a superior high-throughput strategy than lattice energy first principles calculations. The utilization of HSPs in co-crystal screening can be a promising technique once approved utilizing an extent of APIs and co-formers just as researching other readiness strategies and conditions to affirm miscibility as co-crystallization essential. At long last cut-off qualities need reassessment and refinement before this technique become routine in pharmaceutical co-crystal screening. The point of this investigation is to assess the unwavering quality of HSPs to foresee the development of distributed co-crystal of various APIs [27].

Cambridge structural database:

The CSD is a reservoir for small molecule crystal structures. Researchers utilize single-crystal x-ray crystallography to decide the crystal structure of a compound. When the structure is comprehended yet in CSD researchers can look and recover from the database. Researchers can utilize the CSD to contrast existing information and that got from crystal developed in their lab. The data can be likewise used to picture the structure in an assortment of programming, for example atom, powder cell and so on, this is especially significant for analytical reasons since it encourages the identification of stages present in a crystalline powder blend without the requirement for developing crystals [19].

The data gathered in the CSD for every passage can be considered in three classes. Firstly, there is a text based data containing the literature reference, chemical names and blueprints, some trial data about the crystal structure confirmation method and whatever other data that might be accessible for example molecule's uses, colour and shape of crystals and so on. Secondly, there is chemical structure data as a 2D structural illustration which is the premise of a great part of the advanced exploring procedure for the CSD framework. Thirdly, there is a crystallographic data, comprising of unit cell measurements and space group, and atomic co-ordinates. Finally in this third class the genuine estimation of database lies [19].

Differentiation between salts and co-crystals:

For any multi-component crystal to frame there must be some sort of association between the atoms or molecules that make up the Crystal. For the framework to be thought of as multi-component, such interactions are of a non-ionic and henceforth supramolecular type [26]. There is a huge difference between salts and co-crystals; they can be differentiated by the ionization behaviour of primary contents. Co-crystal compositions are predominantly non-ionised and interact through non-ionic interactions, such as hydrogen bonds, pi-pi electrostatic forces. Basically salts has anions and cations, hence they usually interact via ionic interactions [8]. Both co-formers and API could be acid, basic or neutral. Where in ionic components, interactions should remain non-ionic and allows co-crystal formation and not salt formation. The FDA defines a threshold for the differentiation between salt and co-crystal based on the delta pka. If co-crystal contains ionisable groups, it has to prove that co-formers and API exist in their neutral state in the co-crystal and interact via only non-covalent interactions [10].

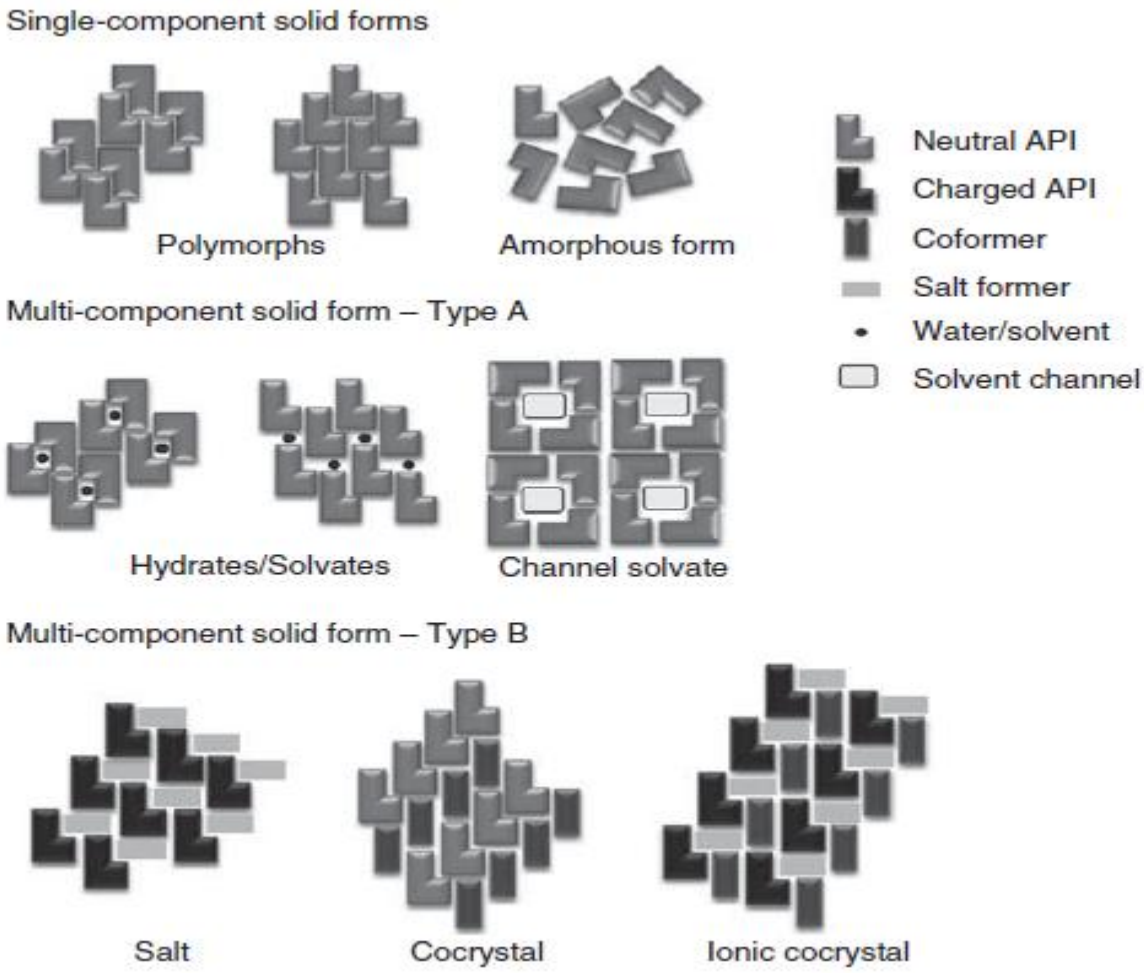

Figure 3: Comparison of multi-component solid form modifications that can be used to alter the properties of API [24].

Mechanism involved in the solubility of co-crystals:

The solubility is majorly dependent on two factors in co-crystals i.e. strength of crystal lattice and the salvation of co-crystals. One can enhance solubility by reducing the lattice energy and/or enhancing the solvent affinity. The co-crystals have the capability to influence both factors to different extent [13].

Methods of preparation of co-crystals:

The preparation of co-crystals can be undertaken by several different methods such as neat grinding, solvent drop grinding/liquid assisted grinding, slurring, solvent evaporation method, anti-solvent addition, supercritical fluid technique, hot melt extrusion, sono-crystallization method, spray drying method, laser irradiation, cooling co-crystallization method, high throughput co-crystallization.

Grinding:

The API and co-former components can be co-crystallized by pulverizing without addition of solvent termed as neat grinding or with few drops of solvent termed as solvent-drop grinding or liquid-assisted grinding [21]. Here the materials are blended, pressed and smashed using mortar and pestle in laboratories where in case of industries, we can pulverize in mill. This method gives particle size decrease yet if there should arise an occurrence of co-crystallization these have turned out to be a feasible technique for Solid State grinding alongside liquid State grinding [31]. The mechanism involved here is the low molecular weight components diffuse easily into the API crystal lattice which could result in formation of intermediate phases such as eutectic or amorphous phase that could further leads to formation of co-crystal [3]. Inability to shape result of co-crystals by grinding might be because of a powerlessness to produce reasonable co-crystal arrangements. Nowadays a recent strategy of adding few drops of solvent to current grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to increased solid state grinding as a method for co-crystal formation [31]. Co-crystallization using neat grinding and liquid assisted grinding method has reported by Shichao Du *et al.* using lamotrigine with isomeric bipyridines as drug and co-formers showed increased solubility and dissolution rate to a greater extent [38]. Mona F. Arafa *et al* has reported co-crystals of felodipine using xylitol as co-former via wet co-grinding method shown greater increase in solubility and dissolution rate [40].

Maciej Przybyłek *et al* has reported co-crystals of salicylamide and ethenzamide using aromatic carboxylic acid co-formers such as acetylsalicylic acid, 4-acetamidobenzoic acid (acedoben) as well as mono- and dihydroxybenzoic acids via droplet evaporation crystallization resulted in increased solubility of salicylamide and ethenzamide by forming heterosynthons [42]. Co-crystals of hydrochlorthiazide using sucralose as co-former via wet co-grinding method is reported by Mona F. Arafa *et al* has shown significant increase in solubility and dissolution rate [44]. Rui-Zhen Lin *et al* has reported solvent assisted grinding method to prepare co-crystals of adefovir using gallic acid as co-former shown greater physical and chemical stability [45]. Inese Sarcevica *et al* used mechanochemical co-crystallization/neat grinding method to prepare co-crystals of isoniazid using benzoic acid as co-former in a stoichiometric ratio of 1:1 which have shown a good physical stability [46]. Sanaa A. El-Gizawy *et al* has prepared the co-crystals of hydrochlorothiazide via liquid assisted grinding with help of aerosil 200 as co-former which enhanced the solubility and dissolution rate of co-crystals [48]. Renu Chadha *et al* has reported solvent drop grinding method to successfully prepare co-crystals of efavirenz with the two different co-formers such as oxalic acid dihydrate and citric acid monohydrate has exhibited 1.8 and 2.7 fold enhancement solubility of co-crystals respectively [17]. Yogesh K. Nalte *et al* has prepared the co-crystals of nevirapine via neat grinding method using maleic acid as a co-former which shown increased solubility of drug [12].

Solvent Evaporation:

Solvent evaporation is the most regular technique in the crystallization process. It is also a predominant methodology in preparing commercial scale pharmaceutical co-crystals to a limited extent, in light of the accessibility of solution crystallization equipment in pharmaceutical manufacturing plants [20]. In this method, both API and co-former are blended with the required solvent sequentially and evaporated totally. During this evaporation process the molecules in solution are required to form hydrogen Bonds. The solvent is selected in such a way that both the API and co-former should show similar solubility in it. If not then one with least solubility than another will precipitate out. One of the main drawbacks of this technique is that it needs more quantity of solvent [31]. Graciela E. Escudero *et al* has reported the co-crystals of sertraline with coumarin 3-carboxylate which is an anti-depressant drug by solvent evaporation method showed significant increase in solubility and dissolution rate [39]. Jianhui Li *et al* has prepared dexlansoprazole co-crystals using isonicotinamide as co-former via solvent precipitation crystallization has shown better solubility [43]. Ranita Samanta *et al* have reported co-crystals of sulfathiazole using 4-aminobenzamide as co-former via solvent evaporation method shown better solubility and dissolution rate [51].

Anti-solvent addition:

It is a precipitation technique of API and co-former. Anti-solvent is termed as any compound that is incapable of solubilised and commonly used anti-solvent is water. Let we take an example preparation of co-crystals of aceclofenac using chitosan, here conformer solution i.e. chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. The prepared dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug [31]. In-Chun Wang *et al* prepared co-crystals of carbamazepine using saccharin as a co-former via anti-solvent approach has given the co-crystals that are significantly higher purity and greater yield compare to solvent evaporation technique. The prepared co-crystals show better physicochemical properties like enhanced solubility and dissolution rate but the selection of appropriate solvent found to be difficult [53]. Nan-Hee Chun *et al* has reported co-crystals of indomethicin using saccharin as co-former via Anti-solvent method and solvent evaporation method, they compared both methods where they found highly pure co-crystals of indomethicin from anti-solvent co-crystallization technique [54].

Super critical fluid technology:

Any substance is characterized by a critical point which is obtained at specific conditions of pressure and temperature. When a compound is subjected to a pressure and a temperature higher than its critical point, the fluid is said to be supercritical. The most commonly used substance is carbon dioxide (CO_2). Utilization of supercritical CO_2 as solvent or an anti-solvent as opposed to utilizing liquid solvents fills in as a great mean for large-scale production of co-crystals [3]. In this technique where an API and co-former are combined by magnetic stirring subsequent to being pressurized by Supercritical CO_2 in a high-pressure vessel. The supercritical anti-solvent (SAS) technique investigates the anti-solvent impact of supercritical CO_2 to precipitate co-crystals from Solutions [31]. Rapid Expansion of Supercritical (RESS) Solutions is an intriguing strategy where both micronization of particles and co-crystallization can be accomplished at the same time utilizing supercritical CO_2 as a solvent. RESS includes no dangerous solvents and in this manner fills in as an eco-friendly technique for a large-scale production of co-crystals. While supercritical CO_2 strategies can be utilized for continuous synthesis of co-crystals, necessity of high pressure and particularly designed nozzles for atomization can restrain the handiness of such techniques for large-scale production [3]. Various methods of supercritical fluid CO_2 to generate co-crystal are:-

(1) Rapid expansion of supercritical solutions (RESS) where CO_2 as a solvent.
(2) Co-crystallization with supercritical solvent (CSS) where CO_2 as solvent and molecular mobility enhancer.
(3) Supercritical anti-solvent crystallization (SAS) where CO_2 as anti-solvent.
(4) Atomization and anti-solvent crystallization (AAS) where CO_2 as spray enhancer or anti-solvent.
(5) Supercritical fluid enhanced atomization (SEA) where CO_2 as spray enhancer or anti-solvent.
(6) Gas anti-solvent crystallization (GAS) where CO_2 as anti-solvent [32].

Co-crystallization using Rapid Expansion of Supercritical Solution (RESS) has reported by Katrin C. Mullers *et al*. using ibuprofen and nicotinamide as drug and co-former. They shown that with RESS, a crystalline micronized co-crystal product with the proper stoichiometric composition can be prepared in a single step operation without the necessity of further processing such as drying or size reduction. In comparison to established size reduction techniques, RESS offers unique qualities such as mild processing conditions and a very low environmental impact due to the absence of organic solvents, which becomes more and more important in today's environment that is increasingly focused on sustainability. Employing RESS produces product that has no toxicity. The rather low throughput rates of RESS can be overcome by continuously running processes with closed loop technique for recycling of the fluid and the use of nozzle arrays, which can open the way for this technique into production. Co-crystal formation via RESS might shows up a greater substitute to established production methods [50]. Some of the major limitations of this technique are requirement of elevated pressure, expensive maintenance cost, need for auxiliary equipments, and thus makes the manufacturing more complicated [14].

High throughput co-crystallization:

High-throughput screening was at one time a main methodology for finding new co-crystals. Sadly, a stage required for the High-throughput screening is costly to obtain. The capital venture on High-throughput screening was defended in early time of pharmaceutical co-crystal research when the science had not been very much created to manage co-crystal screening. Consequently, the possibility of finding another co-crystal is expanded statistically by doing large number of experiments. High-throughput remains a valuable tool to pharmaceutical industry at the present. In any case, it will lose its intrigue when the Science relating to co-crystallization is increasingly developed. Rather, co-crystal design utilizing the supramolecular synthon and retrosynthetic approach is relied upon to grow. In this methodology, a crystal, likewise named supramolecule, is amassed from molecules through explicit intermolecular interactions directed by both chemical and geometric properties of the atoms. The eventual fate of co-crystallization research will essentially profit by the discovery of new synthons, which are structural units for preparing a crystal. At the point when the capacity in crystal structure design and prediction improves, the High-throughput approach will be steadily unimportant [20]. With combined high-throughput screening techniques the speed and efficacy has been greatly increased in searching new pharmaceutical co-crystals without involving the formation of co-crystals [49].

Ultrasound assisted co-crystallization:

Ultrasound has been generally utilized for inciting nucleation in solution and co-crystallizing small molecules. Ultrasound-assisted co-crystallization has a few points of interest over conventional solution crystallization. The mechanical energy discharged while passage of ultrasonic waves prompts primary nucleation at lower supersaturation levels, along these lines decreasing the enlistment time and metastable zone width. Ultrasound can accordingly initiate crystallization effectively from solution which generally is hard to accomplish by conventional solution crystallization experiments [3]. Cocrystallization using ultrasound assisted slurry method has reported by Prafulla P. Apshingekar *et al*. using caffeine and maleic acid as API and co-former increased solubility in water has explained by ternary phase diagram [41].

Hot melt extrusion:

Co-crystallization technique utilizing heat is a novel strategy to frame a co-crystal. It has a few points of interest contrasted with solvent evaporation technique, which is it needn't bother with an organic solvent and can be utilized without drug and co-former solubility determination which is a time taking process [32]. Moreover this technique is majorly depending up on thermodynamic stability of components [31]. Hot-melt extrusion (HME) technique is a strategy that consolidated co-crystal development and drug-formulation process, display a more straightforward approach to fabricate a drug product, include drug and co-former, yet additionally an inert matrix. The heat of HME technique is set for particular temperature in such a way that only matrix is melted. Co-crystal development utilizing HME strategy has practically equivalent to instrument with liquid assisting grinding technique, where a catalyzing agent to improve co-crystal arrangement played by softened/melted framework rather than solvent and the reasonable matrices for HME technique must have a following characteristics [32].

- ✓ It should possess low glass transition (Tg) temperature, usually lower than melting point of co-crystal to guarantee a lower processing temperature.
- ✓ It should involve constrained non-covalent interaction with drug or co-former.
- ✓ It has to show a fast solidification step [32].

Spray drying method:

Spray drying is a quick and ceaseless procedure for solid engineering produces dry powder from solution or suspension utilizing hot air stream. For drug-coformer incongruent dissolvability framework, where pure co-crystal can't be formed utilizing solvent evaporation strategy, co-crystallization utilizing spray drying technique can be utilized as an elective technique. Some examples that exhibit incongruent frameworks are carbamazepine-glutaric acid, theophylline-nicotinamide, urea-succinic acid, caffeine-glutaric acid co-crystal, these components can't produce a pure co-crystal through solvent evaporation strategy, yet effectively structure a pure co-crystal when spray drying technique is utilized [32].

Characterization of co-crystals:

Characterization of co-crystal is crucial part in co-crystal research. The basic physic-chemical properties of co-crystals can be characterised by single crystal x-ray diffraction (SCXRD), powder x-ray diffraction (PXRD), infrared spectroscopy (IR), raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), tetrahertz spectroscopy, thermogravimetric analysis (TGA) and hot stage microscopy (HSM) [6].

Spectroscopic techniques:

Some of the techniques that are used are IR, near IR, raman and tetrahertz spectroscopy. They are used to study and identify molecules mobility, intermolecular interactions and H-bond directed molecular associations and to determine solid state form of API and pharmaceutical excepients. Vibrational spectroscopy is considered as one of simplest techniques to distinguish between polymorphs and co-crystals [11]. They are also performed to identify the hydrogen bond pattern present in multi-component molecular crystal structures [16].

IR is a vibrational spectroscopy, most commonly used to determine chemical confirmation of compounds. It is an effective tool in differentiating co-crystals from salts when carboxylic acid is involved in hydrogen bond formation [6]. Their reports are used to evaluate if the transfer of proton has occurred or not between API and co-formers [16].

Solid state nuclear magnetic resonance (SSNMR) spectroscopy is used to characterise solid phases that cannot be studied by Single crystal x-ray diffraction (SCXRD). It is one of the complementary methods to X-ray diffraction (XRD). Nowadays, high resolution SSNMR has shown to be flexible and powerful tool to characterize pharmaceutical co-crystal. The NMR not only allows for non-invasive, element specific observation of different nuclei, but also eases the identification of chemically distinct sites based on Nuclear magnetic resonance (NMR) chemical shift. Additional structural recognition may be obtained from double quantum ^{1}H MAS NMR [6].

Thermal techniques:

Thermal methods are viewed as imperative in giving noteworthy data when used to characterise single and multi-component amorphous and crystalline structures including crystals and co-crystals, their polymorphs, solvates and hydrates. Differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA) and hot stage microscopy (HSM) are considered to be the major thermal characterization methods of importance for solid forms [11].

DSC is majorly used method for the thermal property. DSC is most preferred method to acquire embracing melting point data and additional thermal data, such as enthalpy of melting point can be obtained simultaneously [6]. In this technique the difference in amount of heat needed to enhance the temperature of sample and reference standard is measured as a function of temperature [11]. Along with characterising, DSC has also used as screening tool for rapid co-crystal screening nowadays [6]. The different transitions of endothermic such as melting, glass transition, dehydration/desolvation and thermo degradation consume heat whereas, transition of exothermic such as crystallization or decomposition releases heat [11]. Alex N. Manin *et al* has assessed the relative screening efficiency of DSC, thermal microscopy and saturation temperature technique, utilizing solvent-drop grinding/PXRD mix as a benchmark. At a beginning time of research, DSC screening is the most proficient technique as it makes it conceivable to screen out the frameworks in which co-crystal development is most improbable before getting co-crystals. The technique informative value increments when it is joined with thermal microscopy which permits conducting a full thermal analysis of the framework [49].

TGA is another major thermal technique based on examining weight loss during heating. It is accounted to be an excellent method to study solid form decomposition. If the co-crystals involve volatile components, this technique become more useful, as quantification of weight loss confirms the stoichiometry. In this advanced method, TGA is attached to a Fourier transform infrared radiation (FTIR) spectroscopy in such a way that the released gas/volatile components enter the FTIR where spectral measurements can be taken with temperature. The TGA-FTIR method is an important advancement for identification as well as qualification of residual solvent and solvates of related crystal and co-crystal forms [11].

HSM is major initial screening technique for observing crystallisation process. It is based on thermal imaging which involves direct optical observation of the crystal or co-crystal solid forms as a function of temperature using a polarizing lens. It is sensitive to transitions in the solid phase such as melting, recrystallization, dehydration and desolvation events. HSM associated to DSC or other spectroscopic method can further increase the application of this technique [11].

X-Ray diffraction technique:

X-Ray diffractometry, which includes PXRD and SCXRD, is a powerful method used for identification as well as stoichiometric determination of crystal, co-crystal, solvates and hydrates.

PXRD may be used to study phase transformation related to amorphous and crystalline phases, as it is very specific towards the crystalline phase. SCXRD is considered as the “gold standard” for structural characterization of crystals, co-crystals, solvates and hydrates. The SCXRD method is based on X-Ray diffraction by the dense electrons in the crystal structure, which makes it comparatively unresponsive to H-atom positions. In this situation, neutron diffraction is an advanced alternative, which gives exact position by making this method an advanced and viable option for identification and qualification of hydrated co-crystals [11]. SCXRD is usually basic characterization method for determination of the solid state structure of co-crystals at an atomic level, the problem involved is a single pharmaceutical co-crystal which is qualifies SCXRD testing cannot always produced, hence PXRD is utilized more frequently to verify the formation of co-crystals [6].

Regulatory views:

Co-crystal has increased huge significance in the pharmaceutical industry with the presentation of regulatory rules. In 2013, the FDA was the principal regulatory organization to distribute direction on the regulatory classification of co-crystal [21]. A key idea in the usage of co-crystals is that there is no alteration in the atomic structure of the API. This was perceived by the FDA in their ongoing direction record in which they explicitly express that "Co-crystals are considered as same as API from a regulatory point of view", a much needed development from years pervious [15].

This could empower pharmaceutical companies to look for FDA endorsement for their medicines utilizing information from past safety and efficacy examinations to put up another product for sale to the market. Pharmaceutical companies can submit applications for medicines with new signs or changes to the strong structure. Along these lines, the FDA has decreased the regulatory and money related weight to support development so patients at last receive the rewards of the most recent restorative advances as quickly as time permits [15].

In Europe, the European Medicine Agency discharged a reflection record in 2015 that arranged co-crystal is a comparative method to salts and API. Under this guideline, it implies that the co-crystal is viewed as equivalent to the API except if it shows diverse Pharmacokinetic properties, a methodology that industry considered progressively satisfactory. There is additionally an open door for generic companies to create novel solid forms to conquer patent protection on existing marketed products [15]. They consider solvates and hydrate as subgroup of co-crystal and breaking point the meaning of co-crystal by expressing that the parts of a co-crystal should exist as individual solids at normal environment conditions [2].

Late gauges put the expense of building up new medicine at USA is 2.8 Billion besides, the quantity of affirmed drugs per billion of going through has divided every year since the 1950s. This eventually drives up expenses and puts further strain on worldwide health care assets. Hence, this crystal engineering can offer an answer in light of the fact that new intellectual property opportunity exist for trend-setters who create co-crystals of new and existing drugs, especially on the off chance that it results in progress of pharmacokinetic properties of API [15].

The fundamental criteria for the patentability of any innovation are novelty, utility and non-obviousness. Patent filing of co-crystal is related with their particular chemical compositions, supramolecular systems in crystal structure and beneficial properties. Fruitful characterization of co-crystal and the evaluation of their pharmaceutical and biopharmaceutical properties are prime contemplations for successful patenting. The count of patents conceded to co-crystals and their techniques for preparing are expanding yearly [21].

Future prospective:

Co-crystallization of ineffectively water-dissolvable drugs is one of the novel approaches to improve their water solubility. A great deal of research endeavours are currently centred on orchestrating co-crystals of inadequately water-soluble APIs with suitable co-formers. Picking a right co-former is of most extreme significance. At present, co-formers are picked dependent on empirical methods. Accordingly, advancement of another and quick co-former screening technique is important to screen co-formers preferable for co-crystallization [3]. Drug–nutraceuticals could be beneficial and generally simpler to create. Most nutraceuticals are weakly ionizing molecules that show poor bioavailability. Various clinical trials are examining the potential advantages of different nutraceuticals in numerous health conditions. Malignant growth and torment related issue could frame a potential stage for the improvement of multidrug nano co-crystals with upgraded bioavailability and quick dissolving capacities to accomplish quicker onset of action [21]. The co-crystallization technique is most beneficial for some drugs which undergo degradation because of certain conditions such as basic or acidic environments or deficient of basic or acidic group for the formation of salt. Nowadays researchers are showing more interest towards co-crystals due its impeccable advantages. It will be nothing unexpected if co-crystals become most significant in the pharmaceutical market [9].

CONCLUSION

Co-crystallization approach is blooming nowadays due to its impeccable effect of solubility on poorly dissolvable drugs, especially those having weakly ionisable group and neutral compounds. Meanwhile co-crystallization will also put an effort into improvement of other physicochemical properties of drugs such as chemical stability, flowability etc. The involvement of neutraceuticals as co-formers is found to be highly successful in terms of treating multiple diseases or to exhibit synergistic effect. The expansion of industrially significant methodologies for the production of co-crystals and using neutraceuticals as co-formers for the additional benefits can be expected in near future.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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