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AN OVERVIEW ON PROPERTIES OF PHARMACEUTICAL COCRYSTALS: REVIEW

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ABSTRACT:-

Co-crystallization alters the molecular interactions and composition of pharmaceutical materials, and is considered better alternatives to optimize drug properties. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. Cocrystals can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and van der Waals forces. Co-crystals High Throughput provides information on relationship between formation and chemical structure of the API and conformer. Factors affecting co-crystal stability are reported and a co-crystal is only expected to form if it is thermodynamically more stable than the crystals of its components. Phase transformations induced during processing/storage affects the mechanisms of conversion of crystalline drugs to co-crystals. Pharmaceutical co-crystals could play a major part in the future of API formulation and can be employed for chiral resolution.

KEYWORDS: Co-crystallization. Heterosynthon. Hydrogen bonding. Pharmaceutical cocrystal. Polymorph.

1. INTRODUCTION:

A drug compound is classified using the biopharmaceutical categorization system according to its permeability and solubility in water [1]. When making decisions on the discovery and early development of new drugs, the Biopharmaceutical Classification System is a helpful resource. By categorizing drug compounds into four classes backed by their solubility associated with dose and intestinal permeability in combination with the dissolution properties of the dosage form, it enables the prediction of in vivo pharmacokinetics of oral immediate-release (IR) medicinal products [2]. The US Food and Drug Administration (FDA) guidelines for the Biopharmaceutical Classification System (BCS) were made available to increase the effectiveness of the drug product development process [3]. The Biopharmaceutical Classification Technique is a system for categorizing medicines according to their permeability and solubility. The US Food and Drug Administration has supplied it as a forecasting tool for intestinal drug absorption. Oral administration is the most suitable and commonly employed route of drug delivery thanks to its simple administration, patient acceptability, cost efficiency, least sterility maintenance, and flexibility in the design of a dosage form. However, the main disadvantage with the formulating of oral drug delivery system lies with their poor oral bioavailability. The oral bioavailability of drug substances lies on several parameters including water solubility, drug permeability across biological membrane, dissolution rate, pre-systemic metabolism [4]. It is a factor that the poor water solubility and dissolution profile of drugs in GI fluid often causes the poor bioavailability. The oral bioavailability of drugs may be improved by increasing the aqueous solubility and dissolution profile of the drug substance in the GI fluids. As far as considering the BCS Class II drugs, the rate-limiting step is the drug release from the formulation in GI fluid and not the absorption from biological membrane; therefore, increase in the solubility may increase the bioavailability of BCS Class II drugs [5]. Only 1% of medication compounds entered the market in the pharmaceutical sector, and this is always due to inadequate biopharmaceutical qualities rather than toxicity or a lack of therapeutic efficacy [6]. Solubility is one of these biopharmaceutical qualities that is a big problem, because of their weak solubility, medications are always useless during production that can be sold. Increasing the solubility of medication ingredients is currently one of the pharmaceutical company's biggest concerns. Particle size reduction is one of the techniques that have been utilized to increase the water solubility of pharmaceuticals [5]. Creating salt emulsification, co-solvent solubilizations, and employing polymers to transport medications that are not highly water soluble are some examples [6-9]. Even though it has been demonstrated that these techniques increase oral bioavailability, their effectiveness depends on the particular physicochemical characteristics of the medications under investigation [10]. Pharmaceutical co-crystal formulation has been increasing interest over the past few years as a potential means of enhancing the bioavailability of medications with poor water solubility. Co-crystal and pharmaceutical co-crystal are two terms that must first be understood. There are several ways to define co-crystals [11]. Co-crystals are defined as structurally homogeneous/heterogeneous crystalline solids that include drug and coformer in specific stoichiometric proportions. The discrete neutral molecular reactants that make up co-crystals are solids at room temperature. According to this definition of co-crystals, a pharmaceutical co-crystal is a mixture in which one of the co-crystals' elements serves as an active medicinal ingredient and the other elements serve as coformers. An active drug hydrate is not a co-crystal, as is evident from the statement, but a solid-state drug hydrate is co-crystalline with a

coformer to produce a co-crystal [12]. The pharmaceutical sector currently places a lot of attention on co-crystal methods. Pharmaceutical co-crystals can successfully enhance the drug substance's solubility, dissolving profile, bioavailability and physical stability, in addition to other crucial features such as flowability, chemical stability, compressibility and hygroscopicity [13].

Because of the ability to tailor the physicochemical properties of the solid while preserving the chemical integrity of the medicine, co-crystals have sparked a great deal of interest in pharmaceutical research and development. Co-crystals are a subset of a larger category of multicomponent crystals, which are made up of two or more molecules that form a uniform crystalline lattice in a stoichiometric ratio that is clearly specified (often referred to as the drug and coformer). The drug and coformer are solid at higher temperatures than other types of multicomponent crystals like salt and solvates, and the intermolecular relationships in co-crystals are non-ionic in nature. Through co-crystallization, the variety of solid forms that can be produced from a medicine significantly expands; the physicochemical properties of co-crystals can change based on the properties of constituent molecules. Solubility, dissolution, moisture uptake, chemical stability, mechanical characteristics, and bioavailability are just a few of the pharmaceutically significant features that can change by cocrystallization. The most frequently praised property in literature is solubility [14].

Figure 1. Formations of co-crystals [14].

1.1 Physicochemical properties of co-crystals

For the creation of APIs, co-crystals' physicochemical characteristics are crucial. Adjusting the physicochemical parameters of pharmaceutical co-crystals during drug development improves the stability and efficacy of the dosage form [15]. Numerous studies have been conducted on physicochemical characteristics such as solubility, dissolution, crystallinity, melting point, bioavailability, and stability. The following list summarizes some important physicochemical characteristics of pharmaceutical co-crystals [16].

1.1.1 Melting point

The temperature at which the solid and liquid phases are in balance determines the melting point, which is a fundamental physical characteristic. The value is calculated using the ratio of the change in fusion enthalpy over the change in fusion entropy because melting point is a thermodynamic process where the free energy of transition is equal to zero [16]. Over a conventional melting point apparatus or the Kofler method, DSC is the preferred approach for getting precise melting point data because it allows for the determination of additional thermal data, such as the enthalpy of fusion [16]. It is a common practice to determine a compound's melting point in order to characterize or identify its purity. However, in the field of pharmaceutical sciences, the melting point also has significant value because of its relationships with water solubility and vapour pressure [15]. Although it was necessary to make assumptions about the entropy of fusion, the melting point has actually been directly connected to the log of solubility [17]. In order to tune an API's aqueous solubility towards a specific purpose, it would be highly helpful to know the melting point of that API before it was synthesized.

1.1.2 Stability

Stability has the great importance during the development of new chemical entity. For the evaluation parameters of pharmaceutical co-crystals, stability also plays an important role. A newly produced co-stability crystal is often tested under four conditions: relative humidity (RH) stress, temperature stress, chemical stability and solution stability. Because the amount of water in the co-crystals might cause quality degradation, the relative humidity stress is used to determine the ideal storage conditions for the product. During investigations involving the sorption and desorption of water, it was discovered that co-crystals performed better [18]. Thermal stress and chemical stability are relatively less studied areas about co-crystals properties. Very few reports were discovered, and the few research conducted demonstrated that thermal stress investigations can be a useful tool for learning more about physicochemical stability [19]. When creating these materials, it is critical to evaluate the co-crystals' chemical stability. According to Schultheiss and Newman, solubility stability is the capacity of the co-crystals' constituents to remain in solution and not rapidly crystallize. Solution stability is a crucial factor in the creation of new drugs. To understand how co-crystals behave in release media, stability tests are conducted in addition to solubility or dissolution experiments [20].

1.1.3 Solubility

An important factor in determining pharmaceutical qualities of co-crystal is its solubility. Salt generation, solid dispersion and particle size reduction are a few traditional techniques for improving weakly aqueous medication solubility [21]. With these strategies, there are limitations in practice. Using pharmaceutical co-crystals is a novel way to alter the physicochemical characteristics of medicinal molecules, such as their solubility and dissolution. Researcher interest in solubility is high [21].

1.1.4 Intrinsic dissolution

It assesses the intrinsic qualities of the drug as a function of the dissolution medium, such as pH, ionic strength, and counter ions, and is independent of formulation effects [21]. Intrinsic dissolution measures the rate of dissolution of a pure pharmacological component from a constant surface area. When the sample is squeezed into a disc or pellet for the intrinsic dissolution test, there should not be any shape changes and the disc needs to stay intact throughout the experiment. The majority of the APIs investigated for co-crystallization are categorized as class II pharmaceuticals under the Biopharmaceutics Classification System (BCS), which have high permeability and low solubility. Therefore, intrinsic dissolution rate is a reliable predictor of API in vivo performance. Even if the intrinsic dissolution rate is a crucial factor to research, it can get trickier with co-crystals. In order to collect and correctly interpret intrinsic dissolution data on co-crystals, a number of aspects must be taken into account, and additional experiments may be required [22].

1.1.5 Bioavailability

Bioavailability is a determination of rate and extent of drugs that reaches to the systemic circulation [23]. The bioavailability of newly formed moiety is determined with the help of animal experimentation. The ultimate goal for co-crystal investigation is to improve bioavailability of an APIs. Animal bioavailability is important for a newly prepared compound. The limited numbers of animal bioavailability studies are available on co-crystals [24]

2. SCREENING OF CO-CRYSTALS

Co-crystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio, the solvents, the temperature, the pressure, the crystallization technique, etc. Experimental screening for co-crystal formers is not trivial. Synthesis/processing of co-crystals can be accomplished via a number of methods, including slow solvent evaporation crystallization from solution, solvent-reduced (e.g. slurring, solvent-drop grinding) and solvent-free [e.g. grinding, melt [(hot stage microscopy)], high throughput crystallization and co-sublimation techniques [25]. Typically co-crystals are prepared by slow solvent evaporation that is only viable if compatible solubility in a given solvent exists between the components comprising the potential co-crystal. The potential benefits, disadvantages and methods of preparation of co-crystals were reported [26]. Solvent drop grinding has been reported to be a cost-effective, green, and reliable method for discovery of new co-crystals as well as for preparation of existing co-crystals [27]. A slurry crystallization technique was used in co-crystal screening of two nonionizable pharmaceutical host compounds, stanolone and mestanolone, with 11 pharmaceutically acceptable guest acids and results demonstrated the importance not only of hydrogen bonding but also of geometric fit in co-crystal formation [28].

Scientists reported the synthesis (via solvent-drop grinding, solution evaporation, or crystallization from solution), crystal structures, and basic physicochemical properties of six co-crystals of piracetam with l-tartaric acid, citric acid, racemic mandelic acid, l-mandelic acid, as well as a piracetam−citric acid ethanol solvate. Compared to piracetam the piracetam−l-tartaric acid co-crystal showed improved hygroscopic properties. Scientists reported that liquid-assisted grinding appears to be a more efficient method of screening for co-crystal hydrates [28]. The combinations and variations of the above techniques may be used to cause co-crystal formation [29]. However, co-crystal screening is difficult to automate and labor intensive. The importance of understanding ‘‘supramolecular synthons’’ in synthesizing co-crystals containing pharmaceutical agents have been reported [30]. Recently, it has been reported that molecules which crystallize with $Z' > 1$ showed a markedly stronger tendency to form co-crystals than compounds that crystallize in the pure form with $Z' = 1$ [31]. Co-crystal formation between caffeine and adipic acid has been reported utilizing the newly developed co-crystal screening method [32]. The carboxylic acid–primary amide supramolecular heterosynthon has been exploited for the generation of pharmaceutical co-crystals containing two active pharmaceutical ingredients that are polymorphic in their pure forms [33]. The factors and conditions governing the formation and stability of co-crystals with different stoichiometry were reported with carbamazepine−4-aminobenzoic acid (CBZ−4ABA) cocrystals as the model system. A 1:1 CBZ−4ABA co-crystal was discovered by the reaction crystallization method and co-crystal characterized by carboxylic acid···acid and amide···amide homosynthons. The stability of 2:1 and 1:1 co-crystals depend on ligand solution concentration and the co-crystal richer in ligand component was more stable at higher ligand solution concentrations [34].

A review of several aspects of co-crystallization involving sulfadimidine with a focus on other drug molecules as co-crystallization partners has been reported [35]. Co-crystal forming abilities of the two anti-HIV drugs (lamivudine and zidovudine) were studied to investigate the general applicability of the retrosynthetic approach in the design of new co-crystals. It was reported that both screening strategies and retrosynthetic methods were appropriate for the discovery of new active pharmaceutical ingredients co-crystals [36]. Trimer co-crystals of cisitraconazole-succinic acid have been prepared and characterized by single-crystal X-ray. The extended succinic acid molecule filled the pocket, bridging the triazole groups through hydrogen-bonding interactions rather than interacting with the more basic piperazine nitrogens. Further, the results suggested that co-crystals of drug molecules have the possibility of achieving the higher oral bioavailability normally observed for amorphous forms of waterinsoluble drugs. In addition, the long-term chemical and physical stability provided by crystal forms was maintained. The co-crystal of the model pharmaceutical compound caffeine with oxalic acid exhibited complete stability to humidity over a period of several weeks [37]. The results on the formation of stoichiometric variations, i.e. co-crystals composed of identical molecular building blocks in different stoichiometric ratios using co-crystals composed of nicotinamide (na) and suberic acid (sub) as co-crystal former suggested that the co-crystal formation occurred in a stepwise manner, wherein the cocrystal (na)·(sub) appeared as an intermediate in the synthesis of the (na)2·(sub) co-crystal [38]. Co-crystal prediction has been reported to include the following steps: (1) determining whether a given set of two or more molecular components will undergo co-crystallization; (2) identifying the primary intermolecular interactions, e.g., hydrogen-bond motifs that will exist within a particular co-crystal structure; and envisioning the overall packing arrangement in the resulting co-crystal structure. The comparison of the spectrum of a co-crystal to coadded spectra of co-crystal formers represents a quick and easy judgment of co-crystal formation (or otherwise). Researchers suggested that compared to infrared, Raman Spectroscopy would be the technique of choice for rapidly checking co-crystal formation [39-41]. Scientists demonstrated

the potential of supercritical fluid techniques which include [the Cocrystallization with Supercritical Solvent technique, the Supercritical Anti-Solvent technique), and the Atomization and Anti-Solvent technique] as screening methods for co-crystals using indomethacin-saccharin co-crystalline system as model system [42]. Pure component solubilities determine the concentration regions to screen for new cocrystals, rather than the stoichiometry of the co-crystal. Based on this, new co-crystals of carbamazepine with isonicotinamide, benzamide and 3-nitrobenzamide, and of cinnamic acid with 3-nitrobenzamide have been reported [43]. Scientists described the use of neat and liquidassisted grinding for screening for hydrated forms of pharmaceutical co-crystals, and liquidassisted grinding was found less sensitive to the form of the reactant (i.e., hydrate or anhydrate) than neat grinding [44]. Results on pharmaceutical co-crystals construction involving theophylline and caffeine as pharmaceutical ingredients and L-malic or L-tartaric acid as pharmaceutical co-crystal formers showed that co-crystal formation occurred under conditions in which all co-crystal components remain saturated [45]. Scientists reported a pharmaceutical co-crystal formed between an inorganic acid and an API, which enabled the development of a stable crystalline and bioavailable solid dosage form for pharmaceutical development where otherwise only unstable amorphous free form or salts could have been used [46]. Novel pharmaceutical co-crystal e.g. norfloxacin saccharinate dihydrate and its co-crystal, norfloxacin saccharinate–saccharin dihydrate, were reported [47]. A role for co-crystal formers as hydrogen bond additives that favor and stabilize specific motifs for the crystallization of new polymorphs has been reported for phloroglucinol and phenazine co-crystals of 1:1.5, 1:1.75, and 1:2 stoichiometry [48]. A co-crystal is only expected to form if it is thermodynamically more stable than the crystals of its components. Computational attempts have been made to predict co-crystal formation [49]. Scientists have observed that liquid-assisted grinding of two enantiomorphic co-crystals resulted in to either formation of a centrosymmetric three-component co-crystal, consisting of the left- and right-handed co-crystal former molecules and the model API or the model API along with the racemic form of the co-crystal former [50]. Grinding together of theophylline and D- or L-tartaric acid produced co-crystals that contained theophylline and the co-crystal former in a 2:1 stoichiometric ratio, wherein caffeine and D- or L-tartaric acid produced cocrystals that contained the two components in a 1:1 ratio 74. Carboxylic acid co-crystals of fluoxetine hydrochloride provided the opportunity to modify physical properties while retaining the salt form in the co-crystal structure [50].

3. MECHANISM FOR CO-CRYSTAL SYNTHESIS

Amorphous phases generated by pharmaceutical processes lead to co-crystal formation during cogrinding and storage [51]. The mechanisms underlying moisture uptake generated cocrystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with co-crystal reactants were exposed to deliquescent conditions involve (i) moisture uptake, (ii) co-crystal aqueous solubility, (iii) solubility and dissolution of co-crystal reactants, and (iv) transition concentration [52]. For carbamazepine: nicotinamide co-crystal synthesis, nucleation and growth of co-crystals were directed by the effect of the co-crystal components on reducing the solubility of the molecular complex to be crystallized [53]. A molecular-level mechanism for two cases of mechanochemical co-crystallization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in early stages of the reaction. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N...I and S...I type and involves the initial formation of finite molecular assemblies, held together via N...I bonds that subsequently polymerize into infinite chains by cross-linking through S...I bonds [54]. Cocrystallizations of exemestane and megestrol acetate improved initial dissolution rates compared to the respective original crystals. The mechanism of dissolution enhancement varied. With exemestane/maleic acid co-crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate /saccharin co-crystal, enhancement was due to the maintenance of the co-crystal form and rapid dissolution before transformation to the original crystal [55].

The mechanisms of conversion of crystalline drugs to co-crystals and factors affecting cocrystal stability were reported. Coformer solution concentration controlled the formation and stability of different stoichiometry co-crystals. Studies with 1:1 and 2:1 carbamazepine-4- aminobenzoic acid co-crystals indicated that the co-crystal richer in coformer was found more stable at higher conformer concentration. Co-crystallization also occurred in solid mixtures of co-crystal reactants. Co-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with various carboxylic acid coformers were formed due to moisture sorption and deliquescence in reactant mixtures. In the solid-state, cogrinding carbamazepine with saccharin or nicotinamide formed co-crystals [52, 56].

4. CHARACTERIZATION OF CO-CRYSTALS

Characterization of co-crystals involves both structure (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) [57] and physical properties (e.g. melting point apparatus, differential scanning calorimetry, thermogravimetric analysis) [58, 59]. The analytical potential of NIR spectroscopy for co-crystal screening using Raman spectroscopy as a comparative method has been reported [60]. A compound-sparing, automated and green differential scanning calorimetric method was developed for rapid co-crystal screening which demonstrated the formation of carbamazepine - nicotinamide co-crystals [61]. Co-crystals of a phosphodiesterase-IV inhibitor with L-tartaric acid were characterized [62]. Cocrystals of (−)-gossypol with a C1-8 carboxylic acid or C1-8 sulfonic acid which are useful as inhibitors of Bcl-2 family proteins and use of co-crystals of (−)-gossypol with a C1-8 carboxylic acid or C1-8 sulfonic acid for inducing apoptosis in cells and for sensitizing cells to the induction of apoptotic cell death were characterized ((e.g. (-)-Gossypol- acetic acid cocrystals)[63]. Single crystals of the 1:1 co-crystal of piracetam and gentisic acid obtained via slow evaporation from acetonitrile. Co-crystal or prepared via grinding or slurrying in water was characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction 20. Plots of pH versus solubility were employed to compare the solubility of molecular salts and co-crystals [64]. Mathematical model was developed that describes the solubility of cocrystals by taking into consideration the equilibria between co-crystal, co-crystal components, and solution complexes and was applied to the phase diagrams of carbamazepine/nicotinamide co-crystal in organic solvents. The dependence of co-crystal solubility on solubility product and complexation constants provided a powerful approach to design co-crystal screening methods and to formulate solutions with co-crystal components where crystallization does not occurred [65]. A method was developed to estimate the co-crystal solubility in pure solvent and co-crystal solubility was found to be directly proportional to the solubility of constituent reactants for carbamazepine, caffeine, and theophylline co-crystals [66]. The phase transformation of API to co-crystal has been shown to depend

on solution and cocrystal chemistry where non-stoichiometric concentrations of co-crystal reactants lead to thermodynamically favorable conditions for co-crystallization. A reaction crystallization method for co-crystal screening and synthesis based on the above principles has been reported as applied to various systems including the generation of co-crystals by moisture sorption.

A new approach to model co-crystal phase diagrams was recently reported and its application to an active pharmaceutical ingredient and glutaric acid co-crystal demonstrated good agreement between calculated and experimental data [67]. The indomethacin-saccharin co-crystal was formed with carboxylic acid and imide dimer synthons interconnected by weak N-H...O hydrogen bonds showed considerably faster dissolution rate than that of the stable indomethacin gamma-form 84. Researchers recently reported a stable API-glutaric acid cocrystal having 18-times-greater dissolution rate in water and three-times-higher blood plasma concentrations [39]. Co-crystals of the API piroxicam were characterized for many carboxylic acids [41]. The scientists provided the foundation to experimentally assess the thermodynamic stability of a co-crystal with respect to its component forms using data for the carbamazepine– nicotinamide system [68]. Co-crystal formation should generally be predictable by comparing the relative stability of the most stable co-crystal and its pure components found on the computed crystal energy landscapes 72. The thermodynamically favored structure prediction of the co-crystals of p-aminobenzoic acid with 2,2'-bipyridine, based only on the atomic connectivity of the component molecules and assumed stiochiometry was reported [69]. The most stable solid form of tiotropium fumarate i.e. a new salt-co-crystal of tiotropium fumarate with fumaric acid structure consisted of matched cations and anions (a salt) together with a nonionized free acid moiety as the co-former (co-crystal), and is unique amongst the large number of tiotropium salts that have been prepared and characterized. The stoichiometry cation/anion/co-former of 2:1:1 corresponded to a simple polymorph of the 1:1 salt, and its identity as a co-crystal has been established by single-crystal X-ray diffraction with some corroborating evidence from the Raman and infrared spectra. A detailed investigation of the bonding and geometry of the three crystalline forms of the fumarate indicated that the hydrogen bonding motifs are very similar, and that conformational differences arising from the packing of the two thiophene rings into the crystal structure is probably important in determining their relative stabilities. A comparison with the structures of other tiotropium salts indicated a correlation of the dihedral angle between the two tiotropium thiophene rings with the stability of the crystal forms [70]. Helical-type of chiral co-crystal of tryptamine and hydrocinnamic acid prepared by crystallization in the presence of different chiral crystals have similar crystal structures, despite spontaneous crystallization itself giving only achiral crystal [71]. Curcumin, the main component of the spice turmeric, has been successfully used as a therapy to treat human multiple myeloma [72].and also has shown to possess antiinflammatory and anti-cancer activities [73]. However, curcumin has extremely poor water solubility and bioavailability. A series of pharmaceutically acceptable co-crystal formers are under investigation to screen for co-crystal formation of curcumin [73].

5. PHARMACEUTICAL CO-CRYSTALS AS INTELLECTUAL PROPERTY

Compared to other classes of solid forms, co-crystals possessed particular scientific and regulatory advantages, and alongside these advantages were intellectual property issues which give co-crystals with unique opportunities and challenges. Researchers reported the importance regarding patents on pharmaceutical co-crystals to the pharmaceutical industry [74]. The value of co-crystals to the pharmaceutical industry should become clearer, mainly with respect to several relevant legal and regulatory issues, as products containing co-crystal technology come out from pharmaceutical development pipelines onto the market.

6. APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution [75-76]. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization [74].

7. CONCLUSIONS AND PERSPECTIVES

Pharmaceutical co-crystals represent a advantageous class of crystal form in the context of pharmaceuticals. Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. Co-crystals are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. The relevance of co-crystals in API formulation includes the ability to fine-tune physical properties, characterization of API, identify and develop new, proprietary forms of prescribed drugs and the opportunity to generate intellectual property. Further research is desirable in order to scale up co-crystal systems and implement manufacturing of final dosage forms on commercial scale. Screening for solid forms is important to guarantee that the optimum form is carried forward in development and to minimize the likelihood of unexpected form conversion. Co-crystals – High Throughput gives vital information on relationship between formation and chemical structure of the API and coformer. Screening of API's with library of co-crystal formers requires further investigations to include all possible coformers. Studies regarding polymorphism of co-crystals should be strength in order to accelerate the development of new pharmaceuticals. Additional developments in screening methodology will further elevate the profile of co-crystals on the pharmaceutical and intellectual property landscapes.

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