Review Article

A REVIEW ON INCREASED THERAPEUTIC EFFICIENCY OF DRUGS BY PHARMACEUTICAL COCRYSTAL APPROACH

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ABSTRACT

Pharmaceutical co crystals are crystalline molecular complexes containing therapeutic molecules. 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 non-ionic 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. Crystalline molecular complexes of two or more neutral molecules, represents a potential route to achieve pharmaceutical materials with improved properties of interest, including dissolution rate and stability under conditions of high relative humidity. Pharmaceutical co-crystals if considered better alternatives to optimize drug properties it could play a major part in the future of API formulation and can be employed for chiral resolution. Thus this article focuses on the increased therapeutics efficiency of drugs by co-crystal formation and further future scopes and intellectual property implication of creating co-crystals.

Keywords: Pharmaceutical co-crystal, co-crystallization, physical property enhancement, polymorphs, Crystal engineering, super molecular synthons.

INTRODUCTION

What are co crystals?

Pharmaceutical active ingredients (APIs) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs.[1]

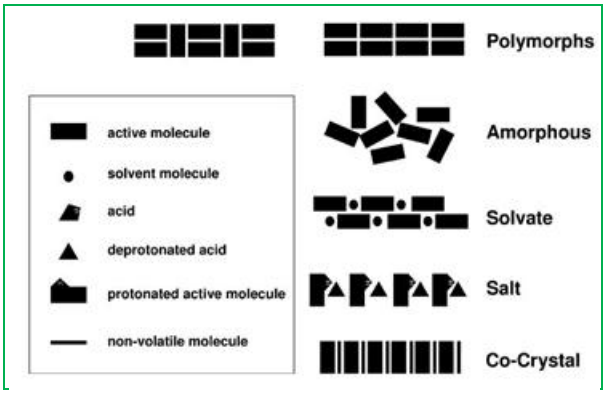

Figure 1: Schematic depiction of various types of solid forms.

Solid form discovery and design depends on the nature of the molecule of interest and type of physical property challenges faced in its development. The preferred solid form is generally the thermodynamically most stable crystalline form of the compound.[2] However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water-insoluble compounds. In this case, alternative solid forms may be investigated. For ionisable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability.[3, 4] Like the parent compound, pharmaceutical salts may exist in several polymorphic, solvated and/or hydrated forms.

Co crystals are multiple component systems where intermolecular interactions and favourable Geometries lead to a self-assembled supramolecular network. Co crystals offer the Advantage of generating solid forms of APIs even when they lack ionizable functional Groups and in this way produce materials with a large range of properties that are not Available in single API solid phases (polymorphs and amorphous forms), or in API Solvates, or salt forms. Solvates are compounds where one of the components is liquid at room temperature, such as a hydrate. In a crystalline salt, the interactions are mostly Electrostatic, and the components are ionized. A pharmaceutical co crystal contains an API and a co former molecule(s), both of which typically exist in the neutral state and interact by hydrogen bonding or by other non-covalent bonds. (A few co crystals have been synthesized in which the API is ionized, but the co former is still non-ionized.[5] The term co crystal generally refers to components that in their pure states are solids at room temperature. Co crystals may include two or more Different components and in most cases to date, two and three component systems are reported with the latter being mostly co crystalline solvates, e.g.theophylline-5-fluorouracil hydrate.[6] Caffeine as shown in figure 2.

The field of crystal engineering has focused on understanding the intermolecular Interactions and connectivities that lead to the construction of super

molecules or extended architectures. Because of its strength and directionality, the hydrogen bond has been the most important interaction in co crystal formation[7]. By studying the hydrogen bond patterns in crystalline solids, valuable knowledge is gained to identify hydrogen-bond preferences and reliable synthons that lead to co-crystal formation. The frequency of hydrogen bond and other important interactions in crystal lattices can be studied by using the Cambridge Structural Database (CSD) by searching for specific molecules, functional groups, and synthons.

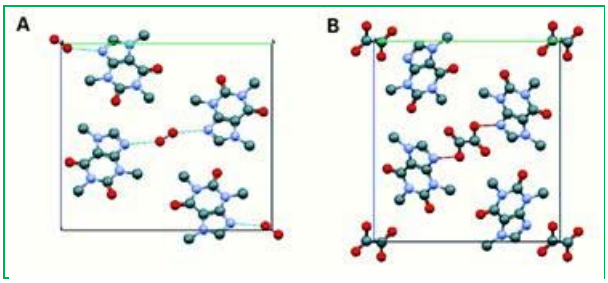

Figure 2: Example of two-component caffeine crystals, the monohydrate (A) and the co-crystal with oxalic acid (B).

The unit cells of the crystals viewed along the a-axis are shown. The hydrate incorporates the solvent (water) molecule in the crystal lattice, while the co-crystal consists of solid compounds. Note that in both structures, the same hydrogen bridges (shown by dotted lines) are involved to connect the host (caffeine) with guest (water or oxalic acid) molecules.

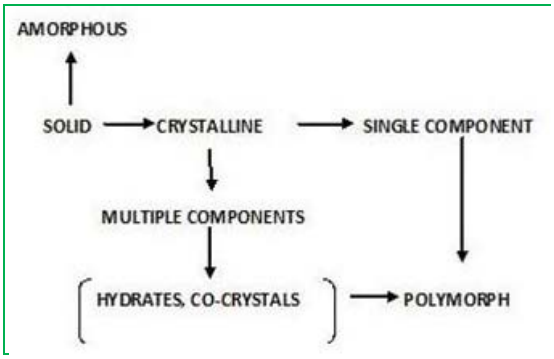

Figure 3: API solid form classification based on structure and composition.

This crystal engineering is generally considered to be the design and growth of crystalline molecular solids with the aim of impacting material properties. Co-crystallization is a manifestation of directed self-assembly of different components. Co-crystals have been described of various organic substances over the years[8,9] and given various names, such as addition compounds[10,11] molecular complex[12,13] and hetero molecular co-crystals.[14] Regardless of naming convention, the essential meaning is that of a multi-component crystal where no covalent chemical modification of the constituents occurs as a result of the crystal formation.

Co-crystals can be constructed through several types of interaction, including hydrogen bonding, p stacking, and vander Waals forces. Solvates and hydrates of the API are not considered to be co-crystals by this definition. However, co-crystals may include one or more solvent/water molecules in the crystal lattice.[15] Co-crystals often rely on hydrogen-bonded assemblies between neutral molecules of API and other component. For nonionizable compounds co-crystals enhance pharmaceutical properties by modification of chemical stability, moisture uptake, mechanical behaviour, solubility, dissolution rate and bioavailability[16].

PROPERTIES

Cocrystal structures exhibit long-range order and the components interact via non-covalent interactions such as hydrogen bonding, ionic interactions, van der Waals interactions and Π-interactions. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components. Such properties include melting point, solubility, chemical stability, and mechanical properties. Some cocrystals have been observed to exist as polymorphs, which may display different physical properties depending on the form of the crystal.

Phase diagrams determined from the "contact method" of thermal microscopy proved valuable in the discovery of new cocrystals. The construction of these phase diagrams is made possible due to the change in melting point upon co-crystallization. Two crystalline substances are deposited on either side of a microscope slide and are sequentially melted and resolidified. This process creates thin films of each substance with a contact zone in the middle. A melting point phase diagram may be constructed by slow heating of the slide under a microscope and observation of the melting points of the various portions of the slide. For a simple binary phase diagram, if one eutectic point is observed then the substances do not form a cocrystal. If two eutectic points are observed, then the composition between these two points corresponds to the co-crystal. The figure 4 shows such example of itraconazole and succunic acid.

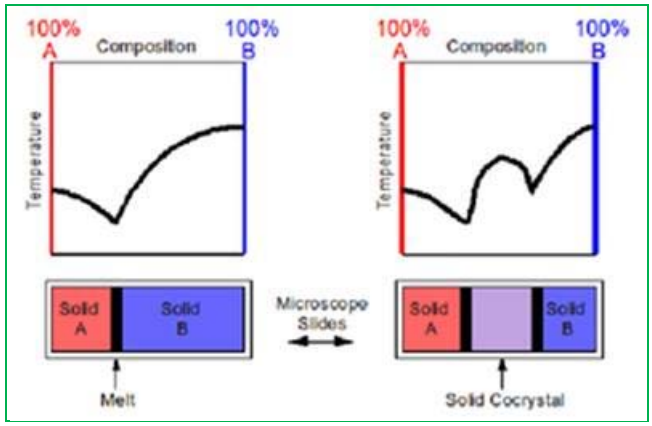

Figure 4: Crystal packing diagram and corresponding unit cell of the 2:1 itraconazole: succinic acid cocrystal. Carbon atoms are large and gray, hydrogen atoms are small and white, nitrogen atoms are blue, oxygen atoms are red, and chlorine atoms are green.

CO-CRYSTALLIZATION AS A TOOL FOR PHYSICAL PROPERTIES OPTIMIZATION OF PHARMACEUTICAL SOLIDS

The main motivation to explore co-crystals of pharmaceuticals is to potentially modify their physical properties, primarily dissolution rate (and hence bioavailability) and hygroscopicity/physicalstability. Hence, this section highlights cocrystallization as a tool for enhancing these specific properties of APIs. With the advent of combinatorial chemistry, API possessing limited aqueous solubility (Biopharmaceutics Classification System Class II drugs) are becoming increasingly prevalent in the research and developments portfolios of pharmaceutical companies. The challenging aspects in development such drug molecules are associated with their slow dissolution in biological fluids and thus insufficient and inconsistent systemic exposure, and consequent sub-optimal clinical efficacy. The traditional approaches (e.g., salt formation, micronization, solid dispersion formulations) to address the issues of poor aqueous solubility often fail to produce a viable solid form as the achieved increase in dissolution rate is insufficient to provide adequate enhancement of bioavailability. In this context, pharmaceutical co-crystals as a distinct solid phase possessing the unique set of properties can be the advantageous alternative to the other solid-state modification techniques. The vivid example demonstrating the success of the co-crystal approach to enhance dissolution rate of APIs is an extremely water insoluble antifungal agent itraconazole. Remenar and collaborators have shown that the cocrystals of itraconazole with various carboxylic acids exhibit a higher solubility and a faster dissolution rate in comparison with those for thefree base. Moreover, the dissolution profile of cocrystals with L-malic acid has matched that of the commercial product (Sporanox) containing amorphous itraconazole.

The stability of a solid API over a wide range of relative humidities is another essential aspect within the pharmaceutical industry as it has practical implications for processing, formulation, packaging, and storage. It is often the case that moisture promotes unwanted solid phase transformations of an API (polymorphic transformations, hydrate formation or crystallization of amorphous phase), which may compromise drug product safety and bioavailability. One approach proposed to inhibit such moisture-induced phase-transformations is rational excipient selection for a specific formulation. In this context, co-crystallization of an API with an excipient can be thought as a more radical strategy to address the issues of poor physical stability of moisture sensitive pharmaceutical materials. For instance, the caffeine/oxalic acid co-crystals have been demonstrated to be superior to caffeine anhydratein terms of physical stability to humidity. Also, an ongoing study in our laboratory demonstrates that co-crystal formation of theophylline with capric or stearic acid can be a promising approach to enhance physical stability of this moisture-labile API. Some other examples of pharmaceuticals co-crystals are presented in table 1.

Table 1: Selected example of pharmaceutical co crystals with their preparation methods with modification of physical properties**.**

API	Co-crystal former	Preparation method	Enhanced property former method (if reported)
Aspirin	4,4'-Dipyridil	Slurry conversion	
Caffeine	Oxalic acid , Glutaric acid	Solvent-assisted, grinding	Physical stability
Carbamazepine	Nicotinamide, Saccharin	Cooling crystallization	Physical stability
Fluoxetine hydrochloride	Benzoic acid, Succinic acid, Fumaric acid	Solvent evaporation	Intrinsic dissolution rate
Norfloxacin	Isonicotinamide	Solvent evaporation	Isonicotinamide Solubility

ADVANTAGES OF CO-CRYSTALS

Co-crystalline form of molecules shows the advantage like stable crystalline form as compared to the amorphous form. In co crystals there is no need to break covalent bonds. The theoretical capability of all types of API molecules either weakly ionizable or non-ionizable increases. In co-crystal there is no need to modify the API. Co-crystal formation improves the solubility, stability, dissolution &bioavailability of drugs from BCS classification. This is the most significant technique and can come over many market problems.

Pharmaceutical coctystallization, which has only recently gained widespread attention as a means of modifying the physiological properties of APIs, has two inherent advantages over other salt form. First, because co-crystal formation may potentially be employed with all APIs, including acidic, basic and non-ionisable molecule and second is a large number of potential 'counter molecules' which may be considered to be non-toxic possibly increasing the scope of the pharmaceutical co-crystallization over the salt forms.

CURRENT MARKET PROBLEMS & SOLUTIONS WITH PHARMACEUTICAL COCRYSTALS

Today in market there is lack of optimum physical properties because of the different nature of APIs and the excipients. The solubility, stability, dissolution rate & bioavailability are the major problems in current market. These current problems can be solved by the formation of Co-crystals.

The design of pharmaceutical crystals that possess different molecular components is valuable to control pharmaceutical properties of solids without changing covalent bonds. Co-crystals, multiple component crystals, often rely on hydrogen-bonded assemblies between neutral molecules of the active pharmaceutical ingredient (API) and other components with well-defined stoichiometry. Therefore, co-crystals increase the diversity of solid-state forms of an API even for non-ionizable APIs, and enhance pharmaceutical properties by modification of chemical stability, moisture uptake, mechanical behaviour, solubility, dissolution rate, and bioavailability cocrystals are being designed and prepared by applying molecular recognition, thermodynamic, and kinetic principles to build hydrogen-bonded molecular assemblies of multiple components. Cocrystals are gaining much interest because the resulting new crystal forms of APIs many times have different pharmaceutical, physical, and chemical properties compared to the original API. Crystal form can be crucial to the performance of a dosage form. This is especially true for compounds that have intrinsic barriers to drug delivery, such as low aqueous solubility, slow dissolution in g.i. media, low permeability and first-pass metabolism.

An analogy can be drawn to salt selection in which pKa arguments are used to select acid-base pairs that can be converted to salt compounds. Chemistry demonstrates that a pKa difference of at least two units (between an acid and a base) is required to form a salt that is stable in water.[17] It is also important to remember that salt formation is generally directed at a single acidic and basic functional group. In contrast co-crystals can simultaneously address multiple functional groups in a single drug molecule. In addition space is not limited to binary combinations (acid-base pairs) since tertiary and quaternary co-crystals are realistic one.[18,19] One very interesting thing was observed that co-crystals provide a powerful means to tailor the desired solubility and dissolution-pH dependence of APIs, even when the API is a non-ionizable molecule.[20]

Significance of Co-Crystal against Solvates

The extent of polymorphism of pharmaceutical is limited to the handful of the different crystal forms. Primary difference between solvates and co-crystals is the physical state of the individual components.[21] If one component is liquid at room temperature then the crystals are designated solvates, whereas if both components are solids at room temperature then the crystals are designated as co-crystals. Solvates are commonplace because they occur as a serendipitous result of crystallization from solution and have the potential to enhance drug dissolution rate, as shown for the solvated forms of spironolactone.[22] Solvated crystals however are often unstable, leading to desolvation during storage and such solvent loss may lead to the amorphous phase crystallizing into less soluble forms. Solvent levels in solvated crystals are also often at concentrations that are not acceptable to regulatory authorities and which may also have toxicological consequences. Co-crystals, however, tend to be a product of more rational design and are more stable, particularly as the co-crystallizing agents are solids at room temperature. As with other crystalline systems, polymorphic co-crystals are not uncommon. At least 20 have been reported to date, including caffeine and glutaric acid[23] polymorphic co-crystals whilst co-crystals are defined by a single phase (miscible) multi-component system in the crystalline state, in the amorphous state they have been referred to as molecular dispersions[24,25] with interactions between the components distinguishing them from solid dispersions.

TECHNIQUES OF PHARMACEUTICAL COCRYSTALS PREPARATIONS

Co-crystals can be prepared by solvent and solid based methods. The solid based methods involve applied to either to wet or dry solid mixtures 80° to 85°[26]

(a) Solvent Based Techniques:

(1) Slurry conversion

(2) Solvent evaporation

(3) Cooling crystallization

(4) Precipitation.

(5) Solution co-crystallization

(b) Solid Based Techniques:

(1) Net grinding

(2) Solvent assisted Grinding

(3) Antisolvent

(4) Sonification

Some of above techniques have discussed below :

(a) Solvent Based Techniques:

1. Slurry Conversion Technique

This is the most convenient method of preparation of co-crystals. This experiment was conducted using different organic solvent and water. Solvent (100 or 200 ml) was added to the co-crystal (20 mg) and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under a flow of nitrogen for 5 min. The remaining solids were then characterized using powder x-ray diffraction method.

2. Solution Co-Crystallization Technique

In co-crystal two components must have similar solubility, otherwise the least soluble component will precipitate out. However similar solubility alone does not guarantee the success full co-crystal formation. It has been suggested that it may be useful to consider polymorphic compounds, which exist in more than one crystalline form as co-crystallising components. If a molecular compound

exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased. Clearly polymorphism alone does not guarantee the functionality of a compound to act as a co-crystallising agent, whilst the ability of a molecule to participate in intermolecular interactions obviously plays a critical role.

Here, small scale preparation has been described. It was performed in a 500 ml of water jacketed glass crystallization vessel. Temperature was maintained by a circulating water bath. A reflux column, digital thermometer, and overhead stirrer with a glass shaft and Teflon blade were attached to vessel ports. The drug and co-crystal former were added to a reaction vessel. The solids were dissolved in ethanol/methanol mixture and heated to 70°C for 1 h under reflux. Temperature was decreased in 10°C increments to induce precipitation in a stirred, unseeded system. Observe the appearance of the co-crystal. Literate to enhance solids recovery decrease the further temperature.

(b) Solid Based Techniques:

1. Grinding Technique

The cocrystal product obtained from grinding is consistence with that obtained from solution. This may indicate that hydrogen-bond connectivity patterns are not idiosyncratic or determined by non-specific and unmanageable solvent effects or crystallization conditions. Nevertheless there are exceptions. Whilst many co-crystal materials can be prepared from both solution growth and solid-state grinding, some can only be obtained by solid-state grinding.

An example is that in the co-crystallisation of 2,4,6-trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were obtained from solution compared with grinding. Failure to form co-crystals by grinding may be due to an inability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. When co-crystal formation has been successful from solution, but not from grinding, solvent inclusion in stabilizing the supramolecular structure may be a factor. Although co-crystal formation by solid-state grinding has been established for some time and a late 19th century report is often cited as the earliest reference to such a procedure, the recent technique of adding small mounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to increased interest of solid-state grinding as a method for co-crystal preparation.

2. Antisolvent Addition Technique

This is the method of recrystallization or precipitation of co-crystal former and APIs. Solvents include buffers (pH) and organic solvents. For example preparation of co-crystals of aceclofenac using chitosan, in which 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. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.

APPLICATIONS OF PHARMACEUTICAL CO-CRYSTALS

➢ **Biopharmaceutics Classification System**

The Biopharmaceutics Classification System (BCS) was developed in 1995 by Amidon and coworkers which correlates *in vitro* drug dissolution and in vivo drug bioavailability. For orally delivered drugs, drug dissolution and permeability in the G.I tract are now understood as mandatory requisites. This formed the basis of the correlation developed. The BCS system classified drugs into 4 categories, based on aqueous solubility and permeability as shown in Table below.

Table 2: The Biopharmaceutics Classification System is based on aqueous solubility and permeability.

Class	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

a) Class I: Represents drugs with high permeability and high solubility.

b) Class II: Represents drugs with high permeability and low solubility.

c) Class III: Represents drugs with low permeability and high solubility.

d) Class IV: Represents drugs with low permeability and low solubility.

Cocrystallization is a very good technique to increase the bulk solubility for drugs with low solubility which belongs to BCS Class II and IV. As discussed above, for example with CBZ which has limited solubility and cocrystallization helped to increase the solubility of the drug. The FDA guidance of BCS which was brought about in 2000, classifies a substance to be highly soluble when the highest dosage is soluble in 250 mL or less aqueous media over pH range of 1-7.5. It classifies a substance to be highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose based on mass balance or in comparison to an intravenous reference dose. Caffeine and Pentoxifylline the two API investigated here are both BCS class I drugs and in this case the solubility of the API's were decreased by cocrystallization.

Cocrystal engineering involves utilizing science to combine and optimize the properties of separate compounds for specific applications such as improving energetic materials, pharmaceuticals, and other compounds. Of these, the most widely studied and used application is in drug development and more specifically,

the formation, design, and implementation of active pharmaceutical ingredients, or API's. Changing the structure and composition of the API will have great influence on the properties and particularly, the bioavailability of the drug. The engineering of cocrystals takes advantage of the specific properties of each component to make the most favourable conditions for solubility that could ultimately enhance the bioavailability of the drug. The principal idea is to develop superior physico-chemical properties of the API while holding the properties of the drug molecule itself constant.

Cocrystal engineering has become of such great importance in the field of pharmaceuticals that a particular subdivision of multicomponent cocrystals has been given the term pharmaceutical cocrystals to refer to a solid cocrystal former component and a molecular or ionic API. However, other classifications also exist when one or more of the components are not in solid form under ambient conditions. For example, if one component is a liquid under ambient conditions, the cocrystal might actually be deemed a cocrystal solvate as discussed previously. The physical states of the individual components under ambient conditions is the only source of division among these classifications. The classification naming scheme of the cocrystals might seem to be of little importance to the cocrystal itself, but in the categorization lies significant information regarding the physical properties, such as solubility and melting point, and the stability of API's.

It is with reasoning that the physical properties of pharmaceutical cocrystals could then ultimately change with varying amounts and concentrations of the individual components. One of the most important properties to change with varying the concentrations of the components is solubility. It has been shown that if the stability of the components is less than the cocrystal formed between them, then the solubility of the cocrystal will be lower than the pure combination of the individual constituents. If the solubility of the cocrystal is lower, this means that there exists a driving force for the cocrystallization to occur. Even more important for pharmaceutical applications is the ability to alter the stability to hydration and bioavailability of the API with cocrystal formation, which has huge implications on drug development. The cocrystal can increase or decrease such properties as melting point and stability to relative humidity compared to the pure API and therefore, must be studied on a case to case basis for their utilization in improving a pharmaceutical on the market.

SCREENING OF CO-CRYSTALS

A screening procedure has been developed and can be done in order to help determine the possibility of the formation of cocrystals from two components and the ability to improve the properties of the pure API. First, the solubilities of the individual compounds are determined. Secondly, the ability of the two components to cocrystallize is evaluated. Finally, phase diagram screening and powder X-ray diffraction (PXRD) are further investigated to find optimum conditions for cocrystallization between the components. This procedure is still done to find new pharmaceutical cocrystals of simple APIs, such as carbamazepine (CBZ), a common treatment for epilepsy, trigeminal neuralgia, and bipolar disorder. CBZ has only one primary functional group involved in hydrogen bonding, which simplifies the possibilities of cocrystal formation that can greatly improve its low dissolution bioavailability.

REVIEW ON RESEARCH DIRECTION

Nanocrystal and Nanopharmaceutical Co-Crystals

A nanocrystal refers to any nanomaterial with at least one dimension ≤ 100nm and it should be single crystalline. The production of drug nanocrystals by bottom up techniques (with main focus on particle diminution by high pressure homogenization) for many new chemical entities of very low solubility has been reported. The transfer of the liquid nanosuspensions to patient convenient oral dosage forms such as tablets and capsules have also been reported. Under microwave irradiation, nonlinear optical nanococrystals of aminonitropyridines with benzenesulfonicacids were reported. Single-component crystalline nanorods, composed of 9-methylanthracene (9-MA) and exposed to a suspension of 1,2,4,5-tetracyanobenzene (TCNB) in water formed a 1:1 charge-transfer complex within the rods, which are transformed from crystalline 9-MA into co-crystalline 9-MA/TCNB. The co-crystal nanorods were characterized by electron microscopy, X-ray diffraction, and optical spectroscopy. These studies demonstrated the importance of organic nanostructures for supporting structure-preserving chemical transformations that were not possible in larger crystals. Nanostructured co-crystals exhibiting single-crystal-to-single-crystal chemical reactivity were constructed by Sonochemistry.

Future Scope:

Attempts to identify reliable supramolecular synthons have for the most part been confined to commonly occurring functional groups such as acids, amides, aromatic nitrogen, alcohol etc. However further investigation of the reliability of supramolecular synthons and hierarchies in a competitive environment may be applied to a wider range185of hydrogen bonding and halogen bonding moieties.

The focus of the presented research has concentrated on the competition between two supramolecular synthons, perhaps investigation of the competition of various hydrogen bonds in the presence of three, four, or even more functional groups should bead dressed as well. Great strides have been made with respect to the generation of binaryco-crystals especially those involving common functional groups, however there is a wide landscape for the formation of ternary or quaternary co-crystals, that remains largely unexplored.

In the context of pharmaceutical co-crystals, the choice of co-crystal formers should be expanded to utilize pharmaceutically acceptable molecules including excipients already utilized in the formulation process. Thus far, there have been limited reports on the physicochemical performance of pharmaceutical co-crystals as compared to the parent API. Consequently the evaluation of physicochemical properties of pharmaceuticalco-crystal is an important area for additional research.

Milling or grinding has long been utilized in the pharmaceutical industry as an effective method of particle size reduction. Many bulk properties such as, flowability bulk density, mixing ability, segregation of mixed materials, bulk density etc. are related to particle size. The determination of bulk properties as a consequence of the method of preparation specifically grinding and/or solvent drop grinding also needs to be addressed.

Additionally, there exists a viable opportunity to apply the solvent-grind and grinding technique towards initial screening and ultimate large scale preparation of pharmaceuticalco-crystals. A temperature regulated High Throughput (HT) grinding or solvent grind screen can potentially lead to the isolation of new phases-polymorphs, co-crystals, salts 186 that may not be viable in a tradition HT crystallization screen.

The phenomenon of polymorphism has long attracted attention, in the case of pharmaceuticals the effect range from issues related to bioavailability to intellectual property. Exhaustive screen involving an HT approach during the preformulation stages could provide more insight toward better understanding the phenomenon and evaluating its frequency. In the context of pharmaceutical co-crystals addressing whether or not pharmaceutical co-crystals are more or less prone to polymorphism may lead to important scientific and intellectual property implications. Additionally, the origins of the polymorphism in pharmaceutical co-crystals and co-crystals in general perhaps require further investigation.

The multi-disciplinary nature of crystal engineering may be expanded to address other molecular targets, such as nucleo bases, proteins and molecules that mimic biologically active compounds etc. Recombinant DNA technology produces a large number of proteins and protein products however these solids are typically produced by precipitation or lyophillization and tend in most cases to be amorphous or partially amorphous. Consequently the stability of protein pharmaceutics presents a problem that may be addressed by applying crystal engineering. The approach towards such biomolecular co-crystals may be multi-fold addressing issues of stability as well as providing models for drug design, and their binding interactions in the solid state. Other molecular targets that would also prove attractive and amenable for study include: molecules with high polarizability to generate new classes of non-linear-optical materials; explosives or propellants with the potential to reformulate and enhance thermal stability etc; agrichemicals and volatile organics. The exploration and crystal engineering of hydrogen bonded 2D and 3D polymers and consequently the use of the hydrogen bonded synthons as precursors to a range of solid state synthetic reaction are other areas that still remain to be chartered.

PHARMACEUTICAL CO-CRYSTALS AS AN 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 **t**he importance regarding patents on pharmaceutical co-crystals to the pharmaceutical industry[27]. 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.

The Importance of Pharmaceutical Cocrystal Patents

As with patents on new molecular entities, patents on pharmaceutical cocrystals may be important to the pharmaceutical industry in a number of key respects.

- ✓ **Commercial Advantages.** A research organization generally files a patent application covering the chemical structure of an API soon after recognizing its therapeutic utility, thereby guarding against another organization independently filing on the same molecule. Accordingly, claims covering the chemical structure of an API often represent the primary patent protection for a marketed pharmaceutical product. In certain cases, however, additional patent protection can be obtained by patenting novel solid forms of the API discovered in development. The decision of when to initiate API solid-form screening can bear on future market exclusivity. If API solid-form screening is conducted at an early stage, an application covering commercially viable solid forms can be filed together with an application covering the API chemical structure. This approach safeguards against other organizations filing applications on the same solid forms or attempting to develop technology which circumvents the product's IP protection. Alternatively, certain benefits and risks can accompany later-stage API solid-form screening. The effort and expense of solid form screening may be postponed until definitive identification of the preferred final form is required for development and/or regulatory purposes. In this scenario, the initial chemical-structure patent application may be followed by filings covering any newly discovered solid forms of the API, thus providing a solid-form patent portfolio encompassing all therapeutically important solid forms of the API,

including polymorphs, hydrates, solvates, salts, and cocrystals. If the FDA-approved product involves one of the new solid forms in this portfolio, then patent protection of the solid form of the approved product may persist after the core chemical-structure patent expires, potentially leading to increased revenue and improved market position.

- ✓ **Patent Litigation.** Cocrystals offer an apparent advantage over polymorphs or hydrates with respect to the legal doctrine of "inherent anticipation". A claimed invention is not novel if it was described in a prior publication; in such cases the publication is said to "anticipate" the claim. A publication can anticipate a claim even if it does not expressly describe the claimed invention, provided that the claimed invention is a necessary consequence of that which was described in the publication: this is the "inherent anticipation" doctrine. The *Schering* V. *Gene* Vacourt case illustrated the extent of this doctrine in the pharmaceutical field.[28] The claimed invention in *Schering* involved loratadine, an antihistamine marketed by Schering Corporation as the drug Claritin. A tissue was the validity of claims directed to descarboethoxyloratadine, a bioactive molecule produced by in vivo metabolism of loratadine.[29] The court held that claims to the loratadine metabolite as a new molecular entity were inherently anticipated by a prior patent that described administration of loratadine to a patient, since the metabolite necessarily resulted from this administration.[30] While *Schering* involved a covalent modification of a pharmaceutical, it is not difficult to foresee its extension to noncovalent API modifications.
- ✓ **Regulatory Issues.** The ANDA is a mechanism introduced by the Hatch-Waxman legislation to reduce the time and cost of regulatory approval for generic products by allowing generic companies to rely on the innovator's clinical trials. Despite this shortcut, regulators require a generic manufacturer to demonstrate that its product is the "same", for FDA purposes, as the originally approved product. According to the most recent FDA draft guidance,[31] a different polymorph or hydrate crystal form of an API may satisfy the "sameness" requirement for ANDA eligibility provided it exhibits comparable stability and bioequivalence. The most recent FDA draft guidance[32] maintains that a different salt form of an API constitutes a change in active ingredient, potentially necessitating the submission of additional clinical trial data (although, in certain cases, reference to previously published clinical data can be sufficient). The requirement of additional clinical studies introduces additional risk and expense for a generic company intending to market an alternative salt form of an approved product.
- ✓ Pharmaceutical cocrystals, by contrast, have not yet been officially addressed from the perspective of generic regulatory approval. In some respects, cocrystals are intermediate between hydrates (which are ANDA-eligible) and salts (which, in general, are not). Like hydrates, cocrystals are nonionic supramolecular complexes; but like salts, cocrystals involve complexation with substances of greater potential toxicity than water. The issue of whether a new cocrystal of a marketed API may be eligible for regulatory approval via the ANDA mechanism will impact the overall utility of cocrystal technology to the generic pharmaceutical industry,

CURRENT MARKETED PRODUCTS

Table 3: Examples of pharmaceutical cocrystals

API	Cocrystal Former	Ratio (API:Ligand)
Carbamazepine	Nicotinamide	1:1
Itraconazole	Succinic acid	2:1
Piroxicam	Caprylic acid	1:1
Caffeine	Oxalic acid	2:1
Theophylline	5-fluorouracil Monohydrate	2:1

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