International Journal of
Chemical and Pharmaceutical Sciences
2012, Mar., Vol. 3 (1)

ISSN: 0976-9390
IJCPS

Crystal engineering technique – An emerging approach to modify physicochemical properties of active pharmaceutical ingredient

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ABSTRACT

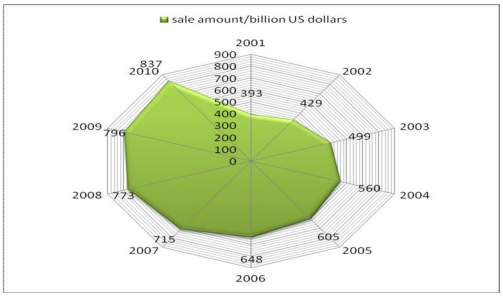
The rising frequency of drugs which having poor solubility, manufacturability and stability in development offers notable risk of new drug products which having low and variable bioavailability particularly for those drugs administrated by the oral route, with consequences for safety and efficacy. Although, number of strategies exists for enhancing the bioavailability of those drugs, these strategies are greatly dependent on the physical and chemical nature of the molecules being developed. Crystal engineering approach presents a number of routes such as co-crystallization, polymorphism and salt formation to improve physico-chemical properties of drugs, which can be implemented through an in detail knowledge of crystallization processes and the molecular properties of drugs. Various polymorphs usually have different physico-chemical, mechanical and thermal properties that can extremely affect the bioavailability, stability and other characteristics of the active pharmaceutical ingredients. This article covers the concept of crystal engineering approach and discusses the potential advantages, disadvantages and methods of preparation of co-crystals, recent advances in the invention and control of the polymorphs of drug molecules, in terms of the development of the selective nucleation of a particular polymorph.

Keywords: Crystal Engineering, Supramolecular Chemistry, Polymorphism and Co-crystals.

1. INTRODUCTION

The international pharmaceutical market has extended at an average annual growth rate of 8 percent since 2001 (Figure no 1), with an expected $ 837 billion in sales in 2010). Especially, over the decades, the extent of the pharmaceutical market at a rate of 17 percent in China has developed [1]. During the development of the pharmaceutical industry, crystallization has been engaged more and more extensively for the purification, separation particle formation and co-crystallization of pharmaceutical materials[2]. It is estimated that more than 70% of all solid drugs are produced by crystallization. With regards to this, an understanding of the effect of the crystallization process on the final solid state of a drug is vital for several of the activities of the pharmaceutical industry [3].

Figure No 1: Annual sales amount of pharmaceuticals worldwide since 2001



Crystal form can be critical to the performance of a pharmaceutical dosage form. This is particularly for compounds that have intrinsic barriers such as low aqueous solubility, low dissolution rate in gastrointestinal media, low permeability and first-pass metabolism to drug delivery to site of action. For water insoluble compounds, the nature of its physical form and formulation tends to demonstrate the utmost effect on its bioavailability profile that needs to be administrated orally in high doses [4].

Active pharmaceutical ingredients (APIs) are frequently delivered in the solid-state as part of an approved dosage form (such as tablets, capsules, etc.) to the patient for treatment. Solid state of API or a drug product provides a suitable, convenient, compact and more stable format to store for long period. Studying and controlling the physico-chemical properties of APIs in solid state, both as pure drug and in formulated products, is therefore an important aspect of the drug development process. APIs can be present in a variety of distinct solid crystal forms, including polymorphs, solvates, hydrates, salts and co-crystals showed in figure 2 [5] . Each solid state form of API displays unique physicochemical properties that can profoundly influence the bioavailability, solubility, chemical and physical

stability, moisture uptake, manufacturability and other performance characteristics of the drug [6].

Over the decade, Advances in crystal engineering and supramolecular chemistry reported from India highlighted the categories of new intermolecular interactions, designed supramolecular architectures, multi-component host–guest systems, cocrystals, network structures, and polymorphs.

This article describes crystal engineering, supramolecular chemistry, co-crystals, polymorphs; mechanism of formation, methods of preparation and application of co-crystals and polymorphs to alter physicochemical characteristics of APIs along with the case studies. The intellectual property suggestions of creating co-crystals by crystal engineering are also highly relevant.

2. Supra molecular chemistry

Supramolecular chemistry is an important, interdisciplinary branch of science encompassing ideas of physical and biological processes, defined as 'chemistry beyond the molecule', i.e. the chemistry of molecular aggregates assembled via non-covalent interactions [7,8]. The term 'synthon' was initially established to explain synthetic organic structural features. The term 'supramolecular synthon' established by Desiraju [9] is defined as: 'structural units within supermolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interaction'.

In biological processes, supramolecular chemistry is nothing but non-covalent molecular binding recognized by Paul Ehlrich and Emil Fischer's lock-and-key principle through concept of complementarity and selectivity. An electropositive hydrogen bond donor move towards an electronegative acceptor, cation···anion electrostatic interaction in metal complexes and salts, and strikes in one part of the molecule fit into hollows of another portion (hydrophobic interactions). While the fundamental recognition processes that guide aggregation of supramolecular are administrated by the same principles and forces, the chemical systems studied are generally classified into two major classes (figure 1): in general molecular recognition in solution is referred to as supramolecular chemistry, and periodic arrangement of supermolecules in the solid state as crystal engineering [10-12].

3. Crystal engineering approach

Crystal engineering defined as 'the understanding of noncovalent intermolecular interactions between the molecules in the context of crystal packing and the utilization of such intermolecular interactions in the design of new solids with desired physical and chemical properties'. In addition, it is recognized that it 'is appropriate increasingly evident that the directionality, predictability, and specificity of intermolecular hydrogen bonds can be utilized to assemble supramolecular structures with controlled dimensionality' [13].

Through the concept of supramolecular synthons, this Crystal engineering approach was brought into the root of organic chemistry, [14] which are repeating periodic arrangement of structural units in crystal structures that are based on hydrogen bond patterns and other non-covalent interaction, able to direct the rational design of supramolecular architectures. Whitesides [15, 16] provide an interpretation of physical organic chemistry to crystal engineering as 'the study of molecular and crystal structure correlation in a family of compounds'. Supramolecular chemistry has developed based on Lehn's analogy that 'supermolecules are to molecules and the intermolecular bond, what molecules are to atoms and the covalent bond' [17]. By connecting atoms with covalent bonds, molecules are built; by connecting molecules with intermolecular interactions solid-state crystals are built. In 1962, the basics of crystal engineering were described by von Hippel in detail under the term 'molecular engineering' [18]. Modern crystal engineering originally commence as topochemistry for understanding the product distribution and regioselectivity in solid-state molecular reactions, [19]. This approach has built rapidly, predominantly with the introduction of modern crystallographic techniques followed by the development of area detector technology. Crystal engineering technique now covers many aspects of intermolecular interactions in solid-state compounds, prediction of structure, control and rationalization, in addition to the novel molecular building blocks synthesis and preparation of crystalline materials, and perhaps packed up into the components of analysis and synthesis [20]. Within the concept of a crystal as a solid state supramolecular entity lies certain key ideas mainstream to the crystal engineering activity.

Crystallization process is concerned with the progress from melt of the crystalline state or supersaturation solution. Within this field primary concerns include the influence of crystallization conditions, the development of crystal nuclei. It is surrounded by the concept of the growth unit that

a discrete link with the supramolecular concept of a synthon is accomplished. This supramolecular synthons are spatial arrangements of intermolecular interactions; therefore, generally the objective of crystal engineering is to recognize and design synthons between molecules that are strong enough to be interchanged between network structures. This ensures simplification eventually leading to the predictability of one-, two- and three-dimensional patterns produced by intermolecular interactions. The Cambridge Structural Database investigation [21] possibly utilized to recognize stable hydrogen bonding motifs [22] with the objective that the strongest motifs will remain intact cross a family of related structures.

Amides and carboxylic acids contain functional groups which are self-complementary and capable of producing supramolecular homosynthons, however they are complementary with each other and can also interact through formation of a supramolecular heterosynthon (Fig. 4). This motif has been considered for in the framework of crystal engineering [23, 24] and the carboxylic acids interaction with heterocyclic bases is possibly the most extensively studied type of synthons [25–29].

4. Polymorphism

Discovery and control of Polymorph is a fundamental problem in pharmaceutical science. Polymorphism refers to a compound that can exist in two or more crystalline forms wherein the molecules have different arrangements (packing polymorphism) and/or conformations (conformational polymorphism) in the crystal lattice [30]. Polymorphism is established to be an extensive phenomenon for most pharmaceuticals [31]. A variety of polymorphs of a drug molecule may have different physical and chemical properties such as stability, solubility, melting point, bioavailability, etc [32]. Stavudine, a thymidine nucleoside is reverse transcriptase inhibitor which act against of the HIV has been exited in two polymorphic forms I (packing polymorphism) and form II (con-formational polymorphism [33]. Polymorph form I has a higher melting point at 170.1°C, while polymorph form II has a lower melting point at 166.6°C. Furthermore, the solubility of polymorph form I is lesser than that of polymorph form II.

The investigation of polymorphism is a most important activity in the practice of crystal engineering today. This subject possibly studied through the crystallization of various forms of crystal and the measurement of their physicochemical properties by analytical techniques such as single crystal X-ray crystallography, powder X-ray diffraction, infrared and Raman spectroscopy, differential scanning calorimetry and modern and exotic techniques such as terahertz spectroscopy. From the point of view of the pharmaceutical industry it is essential to be able to identify very small amounts of one polymorph in the presence of a large excess amount of another. Polymorphism may also be investigated through computational methods. Any crystal structure is linked with energy stabilization with deference to its isolated molecules. This is the energy that should be put into a crystal in order to separate it into its constituent molecules; it is also called the heat of sublimation [34].

The most effective and common method for preparing drug polymorphs is crystallization from solutions or melts [35, 36]. The typical methods for preparing drug polymorphs and solvates are Equilibrium and non-equilibrium crystallization [35–38] (Table 1). Equilibrium crystallization Methods from solution are depended on isothermal or constant-concentration solvent evaporation from a solution in equilibrium with crystals of a given polymorph. Methods of Non-equilibrium crystallization are carried out at significant supersautration conditions in a method owing to rapid variable-temperature crystallization, solvent exchange, and drying by spraying or sublimation.

Key factors that affect the drug polymorphism from crystallization process are degree of supersaturation, temperature, pressure, solution composition, pH of solution, nature of solvent and stirring rate [54]. The factors such as temperature and pressure play a critical role in selection of preparation conditions of a certain drug polymorphs as they define the conditions of their stability, metastability, and solubility [35, 36]. The type of the solvent does not affect directly the free-energy difference of the drug polymorphs. However, choice of solvent can affect the kinetics because of a selective influence on the rate of nucleation and growth of crystals of a certain crystalline modification.

Operating conditions of crystallization can affect in the final crystalline forms. Consequently, a full understanding of the nucleation, crystal growth and phase transformation in the crystallization sequence (Fig. 5) is vital for the control of the polymorphic form. It is recognized that the nucleation process is the principal step in the control of polymorphic crystallization [3].

Fig. No 2: Demonstrating the more common solid-state strategies of the drug and their respected components. Modified from reference [5]

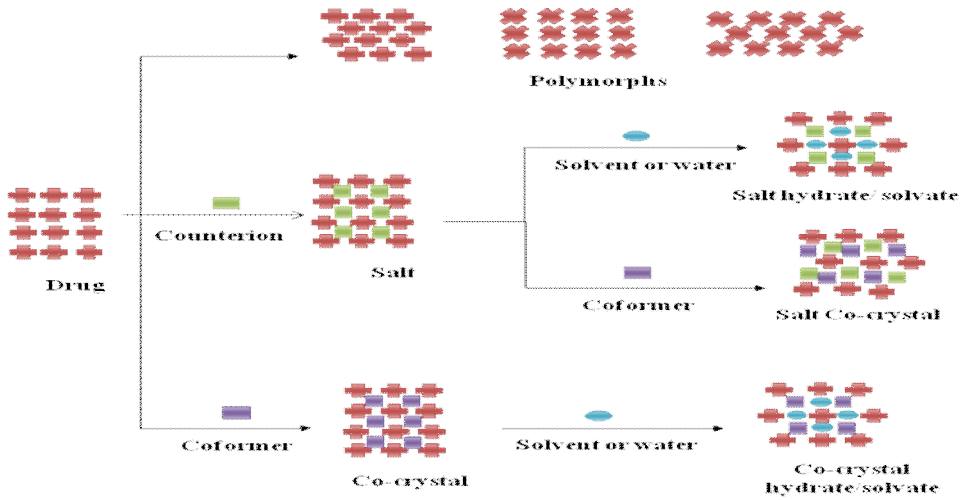
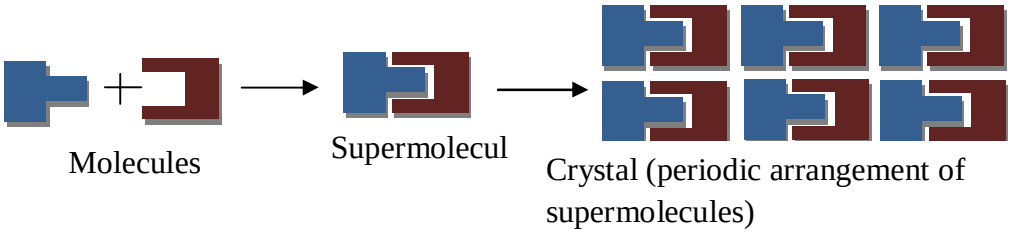


Fig No 3: Supermolecule formation by molecular recognition of molecules and periodic arrangement of supermolecules in **a** crystal lattice. Note the complementary shape and bonding feature of interacting molecules. Modified from reference [12]



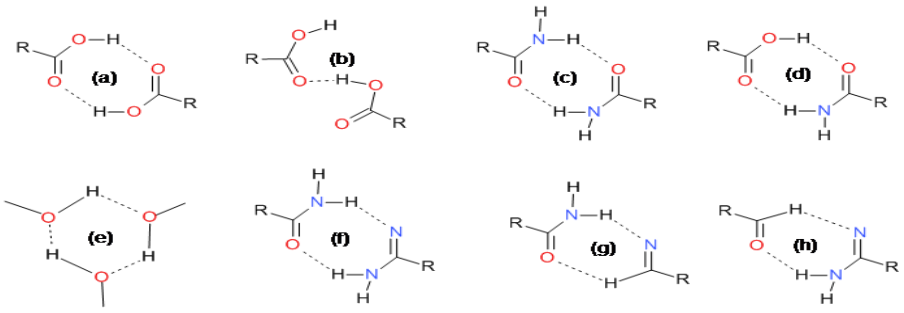


Figure No.4: Showing Representative supramolecular synthons;

(a) homosynthons exhibited by carboxylic acid,

(b) head-to-tail chains formed from carboxylic acids,

(c) homosynthons exhibited by amide dimmers,

(d) heterosynthon exhibited by acid-amide dimers,

(e) six membered intramolecular hydrogen bond ring formed in preference Hydrogen Bonding Rules,

(f) strong synthon with N–H...O and O–H...N interactions,

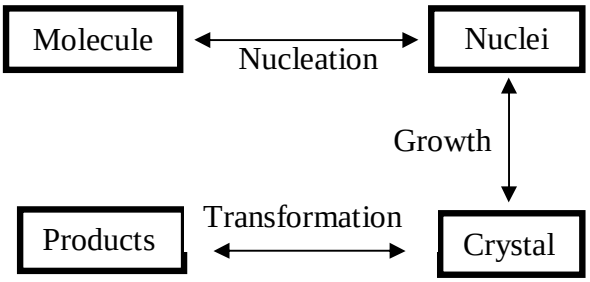
(g) less favoured synthon with one weak C–H...O and one strong hydrogen bond,

(h) weak synthon observed in co-crystals with diols.

Table -1: Equilibrium and Non-equilibrium crystallization Methods for Producing Drug Polymorphs

Method	Principle	Examples	Reference
Polymorphism -Equilibrium Crystallization Methods			
By Equilibrium crystallization from the melt of drug	Slow isothermal crystallization of drug	Pramocaine Chloramphenicol- palmitate	39, 40
Isothermal evaporation of solvent	Slow isothermal evaporation of solvent from a solution in equilibrium with crystals of drug	Prednisolone acetate Phenobarbital Efavirenz Tolbutamide Acyclovir	41- 45
Non-equilibrium Crystallization Methods			
Non-equilibrium crystallization from the melt of drug	Moderately fast crystallization	Paracetamol	46
Polythermal crystallization	Preparation of preliminary hot saturated solution of drug followed by rapid decrease of drug solubility in solution by cooling	Diflunisal	47
Exchange of Solvent	Depended on rapid isothermal reduction of drug solubility in solution by addition of solvent that diminishes the solubility of the drug in the resulting solution	sulfamethoxydiazine, diflunisal histidine Ibuprofen Sodium	47-49
Spray drying	BASED on generating the vital degree of drug supersaturation in a solution dispersed in a gas-heat-transfer stream because of solvent evaporation	Phenobarbital	50
Spraying from supercritical solvents	It involves generating the required degree of drug supersaturation in a supercritical solution upon dispersion because of solvent evaporation	Tolbutamide, Barbital	44, 51
Sublimation drying method	Based on solvent sublimation from a preliminarily frozen drug solution	Pyrazinamide Phenobarbital	42, 52
Crystallization on a surface	A saturated solution or melt in drops placed on various surfaces and films leads to crystallization	Sulfathiazole	53

Figure No 5: Schematic representation of polymorphic crystallization sequence. Modified from reference [3]



4.1. Control of supersaturation

Three of the possible competitive nucleation types of a dimorphic system were shown in figures no 6. For example, the rate of nucleation of polymorph I can be higher than that of polymorph II in whole supersaturation levels (Fig. 6(a)), at high supersaturation levels (Fig. 6(b)), or at both low and high supersaturation levels (Fig. 6(c)). Taking this into consideration, by careful control of the level of supersaturation the desired polymorph can be selectively obtained in some polymorphic systems. For example, at low initial supersaturation (σ) less than 1.5 at the temperature of 20°C, the metastable α polymorph of phenylbutazone nucleates, while the stable δ polymorph occurs at $\sigma \geq 5.0$ [55].

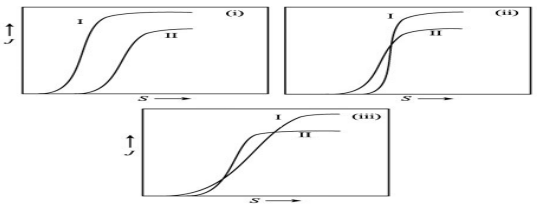


Figure No 6: Schematic graphic of the effect of supersaturation level **S** on the nucleation rates **J** of polymorphs **I** and II. Modified from reference [3]

4.2. Control of temperature in nucleation

One of the predominant and generally considered as operational factors is Temperature that affect nucleation, growth and transformation of polymorphs. The effect of temperature on nucleation has both thermodynamic and kinetic inferences, predominantly for enantiotropic polymorphs [2] such as deliberate or adventitious seeds but sometime possibly overshadowed by other factors.

4.3. Selection of solvent

The selective adsorption of solvent molecules on crystal faces followed by inhibition of nucleation and growth of particular polymorphic forms is credited by the selectivity of solvent upon polymorphs [2], the solvent-solute interactions, etc [56]. A solvent molecule will establish hydrogen bonding with the solute molecule, with its stronger ability to donate or accept hydrogen bonding than the solute molecule, which consequently will result in selective nucleation [57]. For instance, two polymorphs of drug sulfathiazole (II and III) can be obtained in water, two other polymorphic Forms I and IV are crystallized from acetone, even as n-propanol gives only form I [58].

4.4. Seeding technique

During the nucleation phase, Adding seeds of the preferred form are frequently effective to control the product crystal polymorph. Positively the success of this method is significantly dependent upon the "polymorphic recognition" (not merely molecular recognition), which otherwise may effect in the cross-nucleation between polymorphs. For instance, when the alpha polymorph seeds alone were added, the same polymorph of D-mannitol produced, while the seeding of the delta polymorph yielded the alpha polymorph in new growth at small under cooling [59].

4.5. Usage of additives

Occasionally, addition of additives causes an impressive outcome of crystallization [60]. For the period of polymorphic crystallization, structurally similar or related additives may impudence pre-nucleation aggregation processes and/or selectively bind the faces of a growing crystal. By use of tailor-made additives, the design of crystal growth accelerators or inhibitors is possible when the crystal structures of polymorphs are already known [61]. The metastable polymorph V of flufenamic acid (FFA) can experience a rapid interface mediated polymorphic transformation.

4.6. Polymer templating technique

Heterogeneous nucleation happens much more rapidly when the surface introduced can reduce the free energy for nucleation. As a result, heterogeneous nucleation depends on specific interactions such as static forces, hydrophobic interactions, etc between the solute and the surface. A number of different materials have been utilized such as certain polymers including poly(vinylchloride), poly(2,3,5-tribromostyrene), chlorinated polyethylene, poly(tetrafluoroethylene), isotactic polypropylene and nylons. For now, other polymers such as polycarbonate, ethylcellulose, poly(vinyl acetate), etc. ,[62].

4.7. Usage of microporous membranes

Recently, Microporous membranes have been applied in the crystallization processes. For the separation and purification of both inorganic and organic materials, Membrane crystallization is being regarded as a promising technique which is coupled by membrane separation and crystallization [63].

5. Resent case studies of pharmaceutical polymorphs:

The following are the few case studies of pharmaceutical polymorphs of drugs which structures are prepared and solved by crystal engineering approach.

5.1. Polymorphs of Tolbutamide

The anti-diabetic drug Tolbutamide (TB) crystallizes in four polymorphic forms (Forms I-IV), which are differ in their crystal packing mode and in molecular conformation but which are having similar hydrogen bonding synthon (urea tape motif). The first three polymorphs were solved from single crystal X-ray data and Form IV was solved using conventional powder X-ray diffraction (PXRD) data. Thermodynamic stability relationships of polymorphic pairs were evaluated by DSC and graphically visualized in a schematic energy-temperature diagram. Form II is found to be the thermodynamically more stable polymorph and beyond which Form I(H) is the stable polymorph [44].

5.2. Polymorphs of Pyrazinamide

Pure pyrazinamide polymorphs α, δ, γ and mixtures of the β form with one of the other polymorphs were also prepared by crystallization from different solvents, also by lyophilization and sublimation. These forms were completely characterized and clearly distinguishing polymorphs encompassing a dimeric pirazinamide unit, α, β, and δ, and where the dimer does not exist, the γ one. The thermal analysis study of polymorphs demonstrated an attractive scheme of solid phase interconversion. Solid-solid

endothermic phase transitions giving rise to the γ form are observed for the three polymorphs having pyrazinamide dimeric units, being the γ polymorph the stable phase for temperature values higher than ~145 C [52].

5.3. Polymorphs of Caffeine

Polymorphic solid-state transition of caffeine anhydrate from form I (stable at high temperatures) to form II (stable at room temperature) were investigated. The surface phenomena during this solid-state transition were observed by an atomic force microscope (AFM. The transition kinetics was well explained by the penetration model in which the transition developed as the form II structure propagated inward from the crystal surface. The activation energy of this polymorphic transition was determined to be73.8kJ/mol [64].

5.4. Polymorphs of aspirin

All elastic stiffness coefficients, the thermal expansion coefficients and a reliable, internally consistent data set of acetylsalicylic acid have been presented. The elastic stiffness coefficients present a macroscopic demonstration of the anisotropy of the bonding in the crystal. They semiquantitatively predict the elastic behavior of form I and also describe the elastic behavior of form II. This weakens the argument that form II can't be grown because of instability with respect to a small distortion. The explanation of the diffraction patterns initially assumed to represent form II as being due to a domain structure composed of form I and form II is very credible [65].

5.5. Polymorphs of efavirenz

Polymorph, a solvate, and two cocrystals of the anti-HIV drug efavirenz have been prepared, isolated, and structurally characterized by crystal engineering technique. Systematic temperature dependent investigation on single crystals of the nonsolvated form (I) disclose an interesting transformation of single-crystal to single-crystal from an orthorhombic P21212 structure to a monoclinic P21 structure with a associated increase of Z' from 3 to 6 on cooling. A similar transformation was observed in the cyclohexane solvate. A low energy rotation barrier for the cyclopropyl group could be responsible for the aforementioned high Z' structures, as revealed by DFT calculations. Formation of cocrystals of efavirenz seems to be a mostly unpredictable matter. In the cocrystal with 4,4' -bipyridyl, the synthons are more easily predictable [43].

5.6. Polymorphs of Ibuprofen Sodium

Ibuprofen sodium Polymorphs have been effectively micronized with a semicontinuous supercritical antisolvent (SAS) process. Product analyses shows that SAS processing does not cause any contamination or degradation of the product. In addition, it has been exposed that with an sufficient selection of the precipitation rate and supersaturation during the precipitation, which can be restricted by management of parameters such as temperature and ratio of CO2/solution, it is achievable to selectively produce either crystalline particles with rod crystal habit and particle sizes of 1-5 μm, or amorphous spherical particles with particle sizes of about 500 nm [49].

5.7. Polymorphs of Furosemide (Lasix)

X-ray crystal structure of four polymorph of furosemide is reported in the literature and has been characterized. Molecular conformation and hydrogen bonding motifs information on X-ray crystal structures of forms 2 and 3 of furosemide were reported, which present their accurate classification as conformational and synthon polymorphs. Phase transformations demonstrate that metastable form 2 changes to form 1 in grinding and slurry crystallization experiments. The stability of thermodynamic form 1 is demonstrated by its more efficient crystal packing and higher density. A reproducible procedure for growing crystals of form 3 is still awaited. The thermodynamic polymorph of furosemide form 1 having two metastable conformers in the crystal structure provides as a reminder that there is no substitute for crystallization experiments and stability testing of drug polymorphs [66].

6. Co-crystal approach

An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability, is co-crystals through the application of crystal engineering of co-crystals, historically referred to as molecular complexes. The physicochemical properties and the bulk material properties of the API can be modified, at the same time as maintaining the intrinsic activity of the drug molecule. Pharmaceutical co-crystallization is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The intellectual property implications of creating co-crystals are also highly relevant.

This approach of co-crystal involves the expansion of a supramolecular library of co-crystallizing agents. A hierarchy of guest functional groups is classified within the library according to a specific role to a crystal packing arrangement, which is dependent on the host molecule functionalities. These are obtained from investigation of structure property relationships present in the Cambridge Structural Database

(CSD) which contains classes of known crystal structures [29]. Generally in the pharmaceutical industry, Chemists and engineers try to find to deliver crystalline forms of their active compounds, principally due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on isolation and purification of chemical substances [4]. Increasing interest is now receiving to the impact of properties of material on drug discovery and development [67]. The task of pharmaceutical industry is to hastily advance development programs through good confidence with the intention that formulation problems are unlikely to occur and to maximize a compounds potential as a therapeutic. The solid form which is preferred usually the thermodynamically most stable crystalline form of the compound [68, 69]. On the other hand, the stable crystal form of the parent compound may show insufficient solubility and/or dissolution rate which resulting in poor oral absorption, mainly for poorly aqueous soluble compounds. In this case, alternative solid forms may be explored. Preparation of salt forms for ionizable compounds using pharmaceutically acceptable acids and bases is a ordinary strategy to improve bioavailability [4].

A major tool is the hydrogen bond which is accountable for the majority of directed intermolecular interactions in molecular solids. Co-crystals are multi-component crystals depend on hydrogen bonding interactions lacking the transfer of hydrogen ions to form salts. Pharmaceutical co-crystals can be defined as multi-component crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids under ambient conditions.

For nonionizable compounds, co-crystals enhance pharmaceutical properties by modification of solubility, dissolution rate, chemical stability, mechanical behavior, moisture uptake and bioavailability [70]. Recently, Pharmaceutical co-crystallization has only gained widespread attention as a tool of changing the physicochemical properties of drugs, for the reason that co-crystal formation may probably be employed with all drugs, including acidic, basic and non ionizable molecules and a large number of probable 'counter molecules' which possibly considered to be non toxic possibly rising the scope of the pharmaceutical co-crystallization over the salt forms. To salt selection, an correlation can be drawn in which pKa point of view are used to select acid-base pairs that can be converted to salt compounds. Chemistry exhibits that a pKa difference between an acid and a base of at least two units is necessitated to form a salt that is stable in water [71]. In addition, it is significant to remember that salt formation is usually directed at a single acidic and basic functional group. On the contrary co-crystals can concurrently address multiple functional groups in a single API. As well space is not limited to binary combinations that is acid-base pairs as tertiary and quaternary co-crystals are realistic one [72,73].

The key difference between solvates and co-crystals is the physical state of the individual components [74]. At room temperature, If one component is liquid then the crystals are assigned solvates, while if both components are solids at room temperature then the crystals are called as co-crystals. Though, Co-crystals have a propensity to be a product of more rational design and are more stable, predominantly as the co-crystallizing agents are solids at room temperature.

The key remunerations associated with approach of co-crystallization to alter the properties of pharmaceutical solids are the theoretical ability of all types of drug molecules to form co-crystals including weakly ionizable and non-ionizable, and the existence of numerous, potential counter-molecules, including preservatives, food additives, pharmaceutical excipients as well as other drugs, for co-crystal synthesis. Major advantage for the pharmaceutical industry is co-crystal synthesis which may offer is an opportunity to address intellectual property (IP) issues by extending the life cycles of old APIs [75].

7. Advantages of cocrystal approach

Co-crystals having several advantages such as no necessitate to make or break covalent bonds, as compared to amorphous solids it is stable crystalline form, theoretical ability of all types of drug molecules such as weakly ionizable/non-ionizable to form co-crystals, the existence of numerous potential counter-molecules such as food preservatives, pharmaceutical excipients, additives, and other APIs, the only solid form that is designable via crystal engineering patentable expanding IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products [4].

8. General design approaches for co-crystallization

Like to salt screening, Co-crystal screening is a process which is predominantly suited to high-throughput technologies [74]. A pharmaceutically acceptable non-toxic

coformer(s) should be chosen after selection of API for co-crystallization so as to result in a pharmaceutically acceptable product. This restrict the coformers to those that have been approved for consumption by humans, for example pharmaceutical excipients and compounds classified as generally recognized as safe (GRAS) for use as food additives (as classified by the U.S. Department of Health and Human Services).

For each additive, The List of Food Additives Status provides data on limitations to utilize and permitted tolerances. For complete information on a substance's utilize and limitations, reference to the specific regulation for each substance is recommended. The majority GRAS substances have no quantitative limitations as to their levels in food products, although their use must be conventional to good manufacturing practices. Even though GRAS substances are generally recognized as safe in foods, their levels and utilization can be limited in pharmaceutical products.

Where there is no pharmaceutical model use and where the intended additive has no pharmacopoeial monograph, GRAS status does not assurance its use as co-crystal forming agent. Still where precedents exist, the addition of additives is limited to levels established to be safe in existing pharmaceutical products. For instance the maximum additive level of malic acid (which has been co-crystallized with the anti-fungal drug itraconazole) in hard candy is <7% [76]. A number of co-crystals have been formed with co-crystallizing agents classified as GRAS. Though, the required therapeutic level needs to be balanced with the active drug level for a feasible application in drug development and so, except the resulting stoichiometric amount of co-crystal agent is less than the permitted additive level, their pharmaceutical applications will not be realized. Co-crystallization between two drugs has also been proposed as a foundation for both compounds to be pharmaceutically acceptable. This possibly will require the use of sub-therapeutic amounts of drug substances such as aspirin or acetaminophen [73], or the drugs to have similar levels of therapeutic active concentration.

The majority of co-crystallization research has infrequently involved using pharmaceutically acceptable conformers and conditions. The formation of paracetamol adducts with hydrogen-bond acceptors has been reported [77]. Though the co-crystallisation agents used were not GRAS substances, and morpholine and piperazine dihydrochloride as the salt(s) of one or more fatty acids, are only permitted as food additives at the applicable level [78].

9. Co-crystals design

The crystal engineering trials characteristically involves the Cambridge Structural Database (CSD) investigation followed by the experimental work. Co-crystals design based on the principals of supramolecular synthesis; it affords a powerful approach for proactive discovery of novel pharmaceutical solid forms. Co-crystals contains multiple components in given stoichiometric ratio, where different molecular groups interact by hydrogen bonding and by non-hydrogen bonding. The utilization of rules of hydrogen bonding, synthons and graph sets possibly will support in the analysis and design of co-crystal systems. as a general though, prediction of whether co-crystallization will occur is not yet probable and be replied empirically at present. Formation of Co-crystal possibly modernized by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallized. subsequent the broad examination of superior packing preferences and patterns of hydrogen bond in a number of organic crystals, Etter and co-workers projected the rules to facilitate the deliberate design of hydrogen-bonded solids [4].

a. All good proton donors and acceptors are used in hydrogen bonding.
b. Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
c. The best proton donor and acceptor remaining after intramolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors).

These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular cocrystallising agent. A comprehensive thoughtful of the supramolecular chemistry of the functional groups present in a given molecule is the qualification for designing the co-crystals as it assists the selection of the appropriate co-crystal former. Supramoecular synthons that can happen in general functional group so as to design new co-crystals and certain functional groups such as carboxylic acids, alcohols and amides are mainly agreeable to formation of supramolecular heterosynthon [34]. The strong hydrogen bond contains (O-H---O), (O-H---N) (N-H---O), and (-N-H---N). The weak hydrogen bonds involves the –C-H---O and C-H---O=C [15].

Co-crystallization of cis-itraconazole with a series of 1, 4-dicarboxylic acids accomplished of

extended (anti-) conformations were observed [29]. Interaction between succinic acid and the strongest base position of itraconazole though was not present in the co-crystal structure. Co-crystals might not be formed from maleic acid with Z regiochemistry about the C=C bond (with pKa =1.9), or from 1, 3- or 1, 5-dicarboxylic acids. As a result in this case structural fit emerges to be far more significant than acid-base strength complimentarily for successful co-crystallisation. In the relative humidity stability studies of a series of caffeine/carboxylic acid co-crystals [79] it was establish that the oxalic acid which is strongest acid guest molecule produced the caffeine co-crystal of most stable, at the same time as the weakest acid (glutaric acid) produced the least stable cocrystal. Though, a polymorph of the glutaric acid/caffeine co-crystal showed intermediate stability; so pKa alone must not be the only factor dictating co-crystal stability. The exercise of hydrogen bonding rules, synthons and graph sets may support in the design and analysis of co-crystal systems.

10. Methods of preparation of co-crystals

In the literature, formation of Co-crystal described shows the disreputably difficult situation these systems present with regard to preparation it has been recognized to take 6 months to prepare a single co-crystal of appropriate quality for single X-ray diffraction analysis[80]. This is partially as such a heteromeric system will only form if the non-covalent forces between two or more molecules are stronger than between the molecules in the corresponding homomeric crystals. Co-crystal design strategies are still being researched and the mechanism of formation is far from being understood. Co-crystals can be prepared by solid and solvent based techniques. The solvent-based techniques involve solvent evaporation, slurry conversion, cooling crystallization and precipitation. The solid based techniques involve net grinding, solvent-assisted grinding and sonication (applied to both to dry or wet solid mixtures) 80o to 85° [80].

10.1. Co-crystallization from Solution

The two components must have similar solubility for solution co-crystallization; otherwise the component which has least soluble will precipitate out entirely. On the other hand similar solubility of two components alone will not promise success. It has been recommended that it possibly useful to believe polymorphic compounds, which exist in more than one crystalline form as co-crystallizing components. If a molecular compound exists in numerous polymorphic forms it has showed a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Therefore, the possibility of conveying such a component into a different packing arrangement in coexistence with another molecule is improved. Obviously polymorphism alone does not promise the functionality of a molecule to act as a co-crystallizing agent, at the same time as the ability of a molecule to contribute in intermolecular interactions clearly plays a critical role [29].

Co-crystal from Small-scale preparation has been described. Scale-up crystallization was carried out in a water-jacketed glass crystallization vessel and temperature was controlled by a circulating water bath. Teflon blade and overhead stirrer with a glass shaft were attached to vessel ports and also a reflux column, digital thermometer were attached. The API and co-crystal former were added to this vessel and were dissolved in ethanol/methanol mixture and heated to 700 C under reflux for 1 hour. To induce precipitation of co-crystal, temperature was decreased at a rate of 100 C in a stirred, unseeded system. Literate to improve solids recovery decrease the additional temperature [81].

10.2. Co-crystallization by Grinding:

The product acquired when preparing co-crystals from grinding is usually consistent with that obtained from solution. This may specify that patterns of hydrogen-bond connectivity are not idiosyncratic or determined by non-specific and uncontrollable effects of solvent or crystallization conditions. However there are some omissions. at the same time as many co-crystal materials can be prepared from both solution co-crystallization and solid-state grinding, some can only be prepared by solid-state grinding. For instance, in the co-crystallization of 2,4,6-trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were prepared from solution as compared with grinding co-crystallization. Disappointment in co-crystals formation by grinding co-crystallization possibly due to an incapability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. Whilst formation of co-crystal has been successful from solution but not from grinding, may be of solvent inclusion in stabilizing the supramolecular structure. Even though formation of co-crystal by solid-state grinding has been established for a moment and a late 19th century report is frequently cited as the initial reference to such a procedure, the current technique of liquid assistant grinding has been shown to improve the kinetics and facilitate co-crystal formation and as lead to increased attention of solid-state grinding as a method for co-crystallization [29].

Table -2: Resent case studies of pharmaceutical cocrystals

API	Coformer(s)	Description	Reference
Spironolactone (SPI) (nonionizable drug)	Saccharin	It is 1:1 cocrystal hemihydrates, having improved solubility than SPI form II which is most stable	83
Carbamazepine	Saccharin	Solvate formation suppressed by using solvent mixtures, that they reduce the solubility differences between different compounds as compared to pure solvents.	84
Caffeine	Maleic Acid	Reported 1:1 and 2:1 cocrystals together with a new polymorph of maleic acid and rationalize this behavior through measurement of the binary and ternary phase diagrams.	85
	Glutaric Acid	the phase diagram of caffeine-glutaric acid-acetonitrile in the temperature range of 10-35^{0}C was charted using ATR-FTIR and has laid the foundation for further cocrystallization process development of the model system.	86
2-chloro-4-nitrobenzoic acid	Nicotinamide	It is 1:1 cocrystal associated via a carboxylic acid–pyridine hydrogen bond, Thermally more stable than the pure drug.	87
Sulfamethazine	Theophylline	The sulfamethazine molecules form a dimer through the intermolecular hydrogen bonding (O···H-N), and two intermolecular hydrogen bonds (O···H-N and N···H-N) keep the theophylline attached the dimer.	88
Acetaminophen	2,4-pyridinedicarboxylic Acid	Red colored cocrystal discovered by screening using the solution-mediated phase transformation technique.	89

10.3. Co-crystallization by Slurry conversion

Experimentations in slurry conversion were carried out in different organic solvents and water. 100 to 200 ml of Solvent was added and the resulting suspension was stirred at room temperature for few days. After few days, the solvent was decanted and the solid product was dried under a flow of nitrogen for few minutes. The remaining solids were then characterized using PXRD analysis.

10.4. Co-crystallization by addition of antisolvent

This is one of the precipitation methods for co-crystallization of the co-crystal former and drug. In this method, solvents include buffers (pH) and organic solvents. For instance preparation of aceclofenac-chitosan co-crystals, in which solution of chitosan was prepared by soaking chitosan in glacial acetic acid for few hours. By using high dispersion homogenizer the drug was dispersed in chitosan solution. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug [82].

11. CONCLUSION

The design of new crystal form of drugs with application of crystal engineering is an evolving subject. Ability to design new crystal structures will depend mostly on supramolecular chemistry and on viewing a crystal structure with interactions of various types and strengths. Crystal engineering approach involves identification of interactions or supramolecular synthons that will covers an entire family of structures with the object of identifying a set of new crystal forms of API.

The development of new molecular complexes, co-crystal and polymorphs of drugs by crystal engineering is becoming progressively more important as an alternative to salt formation, mainly for neutral or weakly ionizable compounds. Even though lack of priority in marketed products and concerns about the safety and toxicity of co-crystal forming agents, there is raising interest and activity in this area, which aims to increase the understanding of crystal engineering approach.

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