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Review on Crystal Engineering: An Approach for Solubility Enhancement

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ABSTRACT

In the pharmaceutical formulation development field, it is most often required to increase the aqueous solubility of poorly water soluble drugs. It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are as a result of their poor solubility. Review cover crystal engineering technique to overcome these problem by co-crystallization method.

Key word: Solubility, Crystal Engineering, Co-crystallization,

1.0 Introduction

More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug like" properties. It is commonly recognized in the pharmaceutical industry that on an average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics. It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are as a result of their poor solubility. It reduce drug bioavailability. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects of drugs. This is true for parenterally, topically, and orally administered solutions. This achieved by different crystal engineering techniques.

2.0 Solubility

When an excess of a solid is brought into contact with a liquid, molecules of the former are removed from its surface until equilibrium is reached between the molecules leaving the solid and those returning to it. The resulting solution is said to be saturated at the temperature of experiment, and the extent to which solute dissolves is referred to as its solubility.

Solubility is defined in quantitative terms as the concentration of solute in saturated solution at a certain temperature, and qualitatively, it is defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solid phase (Solute).

2.1 Solubility Expression

The U.S. Pharmacopoeia and National Formulary lists the solubility of drugs as the number of milliliters of solvent in which 1 gm of solute will dissolve. Solubility can also be expressed as molality, Mole fraction, percent by weight and percent weight in volume. The descriptive terms of solubility are summarized in table no.1

Table 1 : Descriptive terms of solubility

Descriptive terms	**Parts of Solvent Required for 1 Part of Solute**
Very Soluble	Less than 1
Freely Soluble	1 to 10
Soluble	10 to 30

Sparingly Soluble	30 to 100
Slightly Soluble	100 to 1,000
Very Slightly Soluble	1,000 to 10,000
Practically Insoluble or Insoluble	More than 10,000

3.0 Crystal Engineering

Crystal engineering is generally considered to be the design and growth of crystalline molecular solids with the aim of impacting material properties. A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. Co-crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts this is an important feature, since Bronsted acid-base chemistry is not a requirement for the formation of a co-crystal. Co-crystallization is a manifestation of directed self-assembly of different components. Co-crystals have been described of various organic substances over the years and given various names, such as addition compounds molecular complexes and heteromolecular co-crystals. Pharmaceutical co-crystals can be defined as crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids at room temperature.

Co-crystals can be constructed through several types of interaction, including hydrogen bonding, pi-pi 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. 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 behavior, solubility, dissolution rate and bioavailability. Co-crystals having advantages like stable crystalline form (as compared to amorphous solids), no need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionizable/ non-ionizable) to form co-crystals, the existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs), 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.

3.1 Pharmaceutical Co-crystals

Pharmaceutical co-crystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Co-crystallization offers another option that has enormous potential to provide new, stable structures that may improve the properties of an API. Crystal form screening of APIs has become an integral part of the pharmaceutical industry. This is due to the inherent nature of crystalline forms maintaining stability compared to amorphous forms. Different crystal forms that can be discovered include salts, hydrates, solvates, and co-crystals. Pharmaceutical co-crystals a highly studied subset of co-crystals, afford new crystal forms of APIs and can be defined as, "*a multiple component crystal in which at least one component is molecular and a solid at room temperature and forms a supramolecular synthons with a molecular or ionic API*." Over the years pharmaceutical co-crystals have been studied in the context of improving physicochemical properties including modifying the solubility of the parent API. Crystalline forms of API are sought as they provide stability and also help in the formation of pure products. But these are also subjected to various complications arising from polymorphism, low aqueous solubility, and amorphous nature. The existence of polymorphism for an API creates lots of problems arising from instability during drug formulation. Crystal engineering has created a paradigm to improve these problems. Usually when a new API comes into discovery, and has limited physical properties, it is converted to a salt form of the drug based on the ionizable functional groups in it. Salt formation has been shown to be an effective tool for bettering properties without affecting the biological activity. But the FDA recognizes some 90 acids and 30 bases for salt formation and the presence of ionisable group makes it again a limited approach for neutral molecules.

4.0 Co-crystal Preparation Methods

Table 2 : Methods of Co-crystallization

A) Solid Based Methods	**B) Solvent based methods**
Neat grinding (Co grinding)	Solvent drop grinding
Hot melt extrusion	Antisolvent addition
Twin screw extrusion	Solvent evaporation
	Slurry conversion
	Sonocrystallization
	Solvent mediated phase evaporation (SMPT)
	Supercritical fluid technology

4.1 Solid Base Methods

4.1.1 Neat grinding (Cogrinding)

Neat grinding, is also called dry grinding, consist of mixing the stoichiometric co-crystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. This method requires one or both reactants exhibiting significant vapour pressures in the solid state. To date many kinds of pharmaceutical co-crystals have been successfully synthesised by neat grinding. Various mechanisms have been utilized to describe the process of neat grinding, involving a different types of intermediate phases, such as molecular diffusion, eutectic formation, and amorphous phase, in which one of the three distinct intermediate bulk phases (a gas, a liquid, or an amorphous solid) should exhibit enhanced mobility and/or higher energy of reactant molecules with respect to their starting crystalline forms.

4.1.2 Hot melt extrusion (HME)

Extrusion is a process that involves forcing a raw material or blend through a die or orifice under set conditions such as temperature, pressure, rate of mixing and feed-rate, for the purpose of producing a stable product of uniform shape and density. In this technique the API & CCF is mixed together & then feed into the Hot melt extruder, with different extruder screw configurations & different extruder barrel temperature profiles (at a varying temperature & screw speeds/rpm) & are extruded for the specified period of time. Extruder screw configurations were selected to achieve a range of shearing intensities. HME has grown steadily as an effective method of co-crystallization due to advantages such as being a continuous, single-step, solvent-free and readily scalable process. The novelty of this work is development of a solvent-free continuous process. HME technology is used to produce a pharmaceutical co-crystal using a combination of controlled heat & shear deformation. As it is a continuous process and does not involve the use of extraneous ingredients like solvents, melt extrusion is a cost efficient, effective system.

4.1.3 Twin melt extrusion

Twin-screw extrusion (TSE) of co-crystal components is introduced as a scalable and solvent-less process for manufacture of co-crystals which obviates the need for solution crystallization and it has been demonstrated for the first time using caffeine and AMG 517 as model drugs. It is believed, that TSE offers highly efficient mixing and close material packing, leading to improved surface contact between co-crystal components facilitating co-crystal formation without the use of solvents. Unlike other mechanical mixing procedures, TSE is a continuous process which lends itself to scalability. TSE may be considered as an efficient, scalable, and environmentally friendly process for the manufacture of co-crystals as compared to solvent crystallization methods.

4.2 Solvent based methods

4.2.1 Solvent drop grinding

Liquid-assisted grinding also referred to as kneading, solvent drop, wet cogrinding has made significant improvements in kinetics of co-crystal formation by grinding can be achieved by the addition of minor amounts of an appropriate solvent. The improvements in kinetics might be rationalised by the additional degrees of orientational and conformational freedom open to molecules at the various interfaces as well as the enhancement of opportunities for molecular collisions. In addition, tiny co-crystal seeds may be envisaged to form within the solvent during the grinding process so that the rate of co-crystallisation can be increased. Besides increasing the co-crystallisation rate, the method of solvent-drop grinding (SDG) can control over the polymorphic outcome of co-crystallisation. The nature of solvents using in grinding may have a profound effect on the process of the mechanochemical reaction. The SDG method has been demonstrated to be a novel means of obtaining a particular caffeine-glutaric acid co-crystal polymorph. The choice of solvent used in grinding is important and one basic requirement is that it should be able to dissolve at least part of the original components.

4.2.2 Antisolvent addition

This is one of the methods for precipitation or recrystalization of the co-crystal former and active pharmaceutical ingredient. 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.

4.2.3 Solvent evaporation/ Slow evaporation

Co-crystallisation by evaporation of stoichiometric solutions is the most important tool for co-crystal screening. In order to design successful co-crystal screening experiments, it is very important to consider reactant solubilities. Two co-crystal components A and B have similar solubilities in solvents and the 1:1 pure co-crystal can be formed when equimolar components are dissolved in the solvent by evaporation. To date, many successful co-crystal examples were obtained by this method.

4.2.4 Slurry conversion

Slurry conversion experiments are conducted in different organic solvents 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 PXRD.

4.2.5 Solution co-crystallization/ Reaction crystallization

Reaction crystallization experiments are performed by adding reactant B to a saturated or close to saturated solution of reactant A and then the solution become supersaturated with respect to co-crystal AB, where co-crystallisation proceeds. This method is more effective with nonequivalent solution concentrations and when solutions are saturated with respect to reactants. In one study, Reaction crystallization experiments were performed by adding carbamazepine to saturated or nearly saturated solutions of 18 coformers separately and several pure carbamazepine co-crystals were obtained.

4.2.6 Sonocrystallization (Co-crystallization by Sonication)

“Sonication" and "sonicate" refer to the application of sound including ultrasound. A solid paste may be sonicated in a variety of ways, such as continuously or by one or more pulses. Often one pulse of sonic energy including ultrasound sound is used which is generally on the order of 1 second or less, about 1 to 5 seconds, about 5-10 seconds, or about 10 seconds or more. Sonication applied to a sample by conventional techniques such as by immersing a receptacle containing the sample in an ultrasonic bath, or by placing the tip of an ultrasonic probe directly into the sample or in a well plate (such as a 96-well microplate). The active agents are combined with one or more guests (CCFs) in the solid state. A sufficient amount of a suitable liquid is added to form a solid paste and the resulting solid paste is sonicated to provide a sonicated paste. The suitable liquid of the solid paste provides for a medium by which sonic energy may be transmitted throughout the entire solid paste. By virtue of being a solid paste, the solid particles of active agent and guest have more efficient contact for the transmission of sonic energy than if they were simply physically mixed together.

5.0 Conclusion

Pharmaceuticals having a prominent role in the healthcare of the future and pre-formulation activities need to utilize innovations to respond to the challenges of new discoveries. The newer crystallization techniques provide effective means to discover alternate solid-state forms in complex organic molecules like drugs. These techniques are comprehensive, they are accompanied by enhanced crystallisation rates and they potentially bypass the limitations of additive addition. Ascertaining the metastable forms can prove to be of immense help for those molecules that fail to arrive at the market because of their insoluble temperament. Represent an advantageous class in the context of pharmaceuticals.co-crystal form represent a new type of material for pharmaceutical development and are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs and much more useful in pharmaceutical products than solvates or hydrates. Relevance in API formulation includes the ability to finetune physical properties, characterization of API, identify and develop new, proprietary forms of prescribed drugs and the opportunity to generate intellectual property.

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