A Review on Crystal Engineering of APIs at Microscopic Scale for Enhancement of Bioavailability & Solubility

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Abstract—The crystal engineering of Active Pharmaceutical Ingredients (APIs) at the microscopic scale to enhance their bioavailability and solubility. Many promising new medicines fail because they do not dissolve easily, leading to poor absorption and low bioavailability. Crystal engineering offers a "smart way to fix this problem" by rationally reshaping the solid form of the medicine to achieve desired properties. The primary methods discussed for solubility enhancement include: co-crystallization, solid dispersions, and amorphization. For example, co-crystals, which are distinct solid forms held together by non-covalent interactions, can improve a drug's solubility, dissolution rate, and stability without changing its chemical structure. Advanced characterization techniques such as Powder X-Ray Diffraction (PXRD), Scanning Electron Microscopy (SEM), and Differential Scanning Calorimetry (DSC) are crucial for analyzing these engineered crystal forms. The ongoing challenge is achieving reliable design and long-term stability in these new forms, especially in the pursuit of enhanced drug performance.

Index Terms—Crystal Engineering, Enhancement of Bioavailability and Solubility, Intermolecular Interaction, Co crystal

I. INTRODUCTION

Many promising new medicines fail because they don't dissolve easily in the body Which means the body can't absorb well enough to effective. The crystal engineering is a new and smart way to fix this problem by reshaping the solid form of the medicine to make it dissolve better.1 crystal engineering as a developing field of supramolecular chemistry that focuses on designing and creating new crystal structures with specific desired properties.2

The challenge of creating new drugs that are soluble in water. Many drug molecules fail because they don't dissolve well. Which makes difficult for the body to absorb. To fix this scientists are developing new methods to improve drug solubility. One promising technique involves using nanocrystals to form amorphous nanoparticles. These particles are very small and can be designed to improve stability and solubility of a drug. The researchers making these amorphous nanoparticles using a process called co-crystallization, Which involves combining a drug with another substance to improve its properties. They also used freeze-drying to make a stable and easy-to-use powder.3

The compound ketoconazole (KTZ) is a powerful antifungal agent. It's especially effective against surface infections caused by Candida albicans. KTZ works by inhibiting a key enzyme, Which messes with the fungus's ability to create ergosterol , an essential component of its cell membrane. While KTZ is great for treating fungal infections, it has a major drawback: it doesn't dissolve well in water. This is a big problem because a drug's effectiveness depends on how well the body can absorb it. The poor solubility of KTZ leads to low and inconsistent absorption, Which is bad for its bioavailability. To fix this, scientists are looking into cocrystals and salts. These are new forms of a compound that are created by combining the active drug molecule with other substances. This process changes the drug's physical and chemical properties, like its solubility, Which can significantly improve how well the body Absorbs it.4

Active pharmaceutical ingredients Which are the main active parts of a drug. That a drug's effectiveness depends on its physical properties, like how easily it dissolves, its melting point, and its stability. These properties are influenced by how the drug molecules are arranged, Which is called their crystal form or polymorph. A drug can exist in different crystal forms, and each form can have a different effect on the drug's performance in the body.

Cocrystals are a special type of crystal form where two or more molecules are bonded together in a specific way. That cocrystals are becoming more popular in drug development because they can improve a drug properties. A major goal in drug manufacturing is to create stable and effective forms of a drug. A cocrystal can change its properties for the better, potentially improving how well the drug dissolves or its overall stability.5

Substances that increase the therapeutic effect of a drug without having a medicinal effect of their own. That substance improve the bioavailability of a drug Which is the amount of the drug that gets absorbed into the bloodstream. It also mentions that bioenhancers can reduce the required dosage of a drug minimizing side effects and the cost of Treatment. The drug discovery strategy that uses structural information to design new drugs. It contrasts Respiratory Drug Delivery (RDD) with the use of bioenhancers. The RDD has had some success but is also limited by factors like poor solubility and low bioavailability Which lead to many potential drugs failing in clinical trials. It emphasizes the potential of bioenhancers to overcome these limitations.6

The process of protein crystallization Which is a crucial first step in structural biology studies. By crystallizing a protein, scientists can determine its 3D structure using techniques like X-ray crystallography.7

The document discusses two ways to look at solubility:

Quantitative: This is about measuring the exact amount of a solute that can dissolve. The amount is determined under specific conditions like a certain temperature and Pressure.

Qualitative: This focuses on the nature of the substance and how its properties like its melting point and particle size affect how well it dissolves.8

Co-crystallization is a method used in pharmaceutical drug development to create a more effective version of a drug active pharmaceutical ingredient (API). The co-crystal is a distinct solid form that has different physical and chemical properties from both the original API and the co-former. This new structure is what gives the drug its improved characteristics.9

Crystal's as a way to improve drug properties. More than 40% of marketed drugs and over 70% of new drug candidates have poor solubility, Which affects how well they can be absorbed by the body. The main benefit of using cocrystals is that they can improve a drug solubility, dissolution rate, and stability. This is because they can change the drug physical properties without altering its chemical structure.10

Solubility refers to a drug ability to dissolve in a solvent, like the fluids in our gastrointestinal (GI) tract.

Permeability is the drug ability to be absorbed from the GI tract into the bloodstream.

Bioavailability is the proportion of the drug that enters the circulation and is able to have active effect.11

That a significant number of new drug candidates have poor solubility, meaning they don't dissolve well in water. This is a big problem because a drug needs to dissolve to be absorbed by the body and have its intended effect. The poor solubility of these drugs leads to low and inconsistent absorption and can even cause them to fail during development.12

Solubilizing drugs that don't dissolve well is a major challenge in creating new medicines. Improving a drugs solubility is crucial for getting it into the body and making it effective. Poorly soluble drugs have trouble getting through the cell membranes of our bodies and into the bloodstream. This means that even if a person takes a drug their body might not be able to absorb it properly, making the medicine less effective.13

Pharmaceutical crystallization is a crucial process in drug development that focuses on converting active pharmaceutical ingredients (APIs) from a bulk material into a more useful form for oral drugs. The main goal is to improve the bioavailability of the drug, Which is its ability to be absorbed and used by the body. This process is complex because the API's form, and its corresponding properties, directly affect how well the drug works. The physical form of an API, Particularly its crystalline structure, is very Important. Slight changes in this structure can drastically alter the drug's properties. For example, some crystalline forms may dissolve more easily in the stomach, leading to better bioavailability, while others may be more stable, extending the drugs shelf life.14

Many promising new drug candidates are not very soluble, Which makes it difficult to formulate into effective medications. To overcome this, that are various methods to enhance the solubility of these drugs. One key approach involves using modern techniques to create amorphous or disordered forms of the drugs, Which tend to be much more soluble than their crystalline forms. This is a critical area of

research because improving solubility can lead to better drug absorption and ultimately, more effective treatments.15

A drug must first dissolve in the gastrointestinal (GI) tract to be absorbed into the bloodstream and reach its target. If a drug has poor solubility or is not absorbed well, it can lead to low bioavailability. This means that a large dose might be needed to get the desired therapeutic effect. Which can be a significant challenge in drug development.16 The quantitative amount of solute that can dissolve in a specific solvent at a given temperature. The solubility can be described qualitatively (e.g.,very soluble, sparingly soluble) or quantitatively (e.g., grams per liter). A saturated solution is one where the solute is in equilibrium with the solvent, meaning no more solute can be dissolved.17

1.1 SOLUBILITY:

There are different ways to improve drug solubility, such as making them into smaller particles and using different drug delivery systems. The goal is to increase the amount of drug that the body can absorb, making the medication more effective.18 Solubility depends on the specific solute and solvent as well as factors like temperature and pressure. The amount of solute that can dissolve at a specific temperature is known as its saturation concentration.19

Biopharmaceutics Classification System (BCS)

BCS Class I: Drugs are highly soluble and highly permeable, meaning they are easily absorbed and have good bioavailability.

BCS Class II: Drugs are highly permeable but have low solubility. This poses a challenge in drug Development because they don't dissolve well, Which can limit their absorption.

BCS Class III: Drugs are highly soluble but have low permeability, making it difficult for them to cross biological membranes.

BCS Class IV: Drugs have both low solubility and low permeability, making them the most challenging class to work with for drug development.20

1.1.1 Techniques for Solubility Enhancement.

There are 3 main ways to improve solubility of drugs:

1.Physical modifications:

• Make drug particles smaller (micronization, nanosuspension).

• Change the crystal form (polymorphs, amorphous, cocrystals).

• Mix drug with carriers (eutectic mixtures, solid dispersions, solid solutions).

2.Chemical modifications:

• Change the pH.

• Use buffers.

• Make salts or complexes of the drug.

• Chemically modify the structure (derivatives).

3.Miscellaneous (other methods):

• Supercritical fluid method.

• Use surfactants, stabilizers, cosolvents.

• Use advanced carriers like cyclodextrins, hydrotropy, and novel excipients.21

1.1.2 Importance of improving solubility:

Aqueous solubility is a very important for small-molecule drug candidates.

Poor solubility → poor absorption, even if drug crosses intestine well.

Risk assessment of poorly soluble drugs is hard → low exposure + reduced sensitivity.

High drug concentrations in body → crystallization & possible toxicity.

Poor solubility = major cause of drug development failure.

Clinically acceptable solubility depends on dose size + stomach fluid volume.22

1.2 BIOAVAILABILITY:

Bioavailability is a crucial concept in pharmacology defining the amount and rate Which active drug enters the bloodstream and becomes available at target site.

The bioavailability is measured by concentration of the drug in the blood over time. A challenge is that many drugs especially poorly soluble ones have low bioavailability. This is problematic because it can lead to inconsistent therapeutic effects requiring higher doses Which in turn increases the risk of side effects and costs. Improving a drugs solubility is a primary strategy to enhance its bioavailability and ensure it works effectively, safely, and predictably.23

Nanocrystals are small drug particles, usually between 10 and 1,000 nm in size. It

Like taking a large, coarse sugar cube and grinding it down into super-fine powder. This process called "nanonization," significantly enhances a drugs effectiveness.

Increased Surface Area: By making the particles tiny, nanocrystals have a massive surface area compared to their larger counterparts. When you swallow a drug, it

has to dissolve in the fluids of your stomach and intestines before it can be absorbed. The increased surface area of nanocrystals allows the drug to dissolve much faster and more completely, Which means more of it gets absorbed into the bloodstream.24

1.1.1 Technique for improving bioavailability:

Solid self-emulsifying drug delivery systems

S-SEDDS has been widely studied for the enhancement of Solubility and dissolution of various poorly soluble drugs.

Most Common Method: You take a liquid form of the medicine and a "solid carrier" (like a powder made of corn starch, sugar, or a special type of sand). Then, you use a special machine (a spray dryer) to turn this mixture into a fine powder.

Other Methods: It can simply mix the liquid medicine with an absorbent powder until it becomes a dry powder. One example given is mixing a meloxicam liquid with a special powder made from silicon and magnesium. You can melt a mixture of the medicine and other ingredients, and then let it solidify with a polymer (like a type of plastic) to form a solid block.20

II. LITERATURE REVIEW

2.1 INTERMOLECULAR INTERACTION :

Intermolecular interactions are the attractive and repulsive forces that exist between molecules. Think of them as the "glue" that holds molecules together to Form liquids and solids. They are much weaker than the intramolecular forces, which are the strong bonds (like covalent or ionic bonds) that hold the atoms together within a single molecule. These forces are fundamental to crystal engineering, which is the process of designing and creating new solid materials with specific properties by controlling how molecules pack together in a crystal lattice. The type and strength of intermolecular interactions determine the final arrangement of molecules in a crystal.25

Intermolecular forces (IMFs) are the attractive or repulsive forces that exist between molecules, not to be confused with the much stronger intramolecular forces (like covalent or ionic bonds) that hold atoms together within a molecule. You can think of IMFs as the "stickiness" that causes molecules to clump together, which explains why substances exist as solids, liquids, or gases. The stronger the IMFs, the more energy is required to pull the molecules apart, leading to higher boiling and melting points.26

The strength of these forces directly impacts a substance's physical properties.

Boiling and Melting Points: To change from a liquid to a gas or from a solid to a liquid, molecules must gain enough energy to overcome the IMFs holding them together. Substances with stronger IMFs require more energy to break these attractions, resulting in higher melting and boiling points. This is why water (with hydrogen bonds) boils at a much higher temperature than methane (with only weak London dispersion forces).

Solubility: The rule of "like dissolves like" is based on intermolecular forces. Polar substances tend to dissolve in polar solvents, and nonpolar substances dissolve in nonpolar solvents, because the IMFs between the solute and solvent are similar.27

2.1.1 Methods of Intermolecular interaction:

Nondirectional Forces

Nondirectional forces, which are typically weak (2-10 kJ/mol), include interactions like C-C, C-H, and H-H. The importance of each interaction in a crystal depends on the ratio of carbon to hydrogen atoms. For example, compounds with many carbons and few hydrogens, like aromatic compounds, tend to have a stronger stacking tendency because it maximizes C-C interactions. The C-H interaction is common in many Different types of compounds, both aromatic and aliphatic. In flat aromatic molecules, these interactions can lead to a specific T-shaped herringbone synthon.

There's an ongoing debate about whether certain C-H contacts—specifically those involving a very acidic C-H group, like in alkynes, with pi (π) systems—should be called C-H…π hydrogen bonds. The alternative view is that they are simply an extreme case of the regular C-H herringbone interaction.

Hydrogen bonding

A hydrogen bond is a special and very reliable attraction between molecules. It's not a strong, permanent chemical bond like the ones that hold atoms together inside a molecule. Instead, it's a powerful "sticky" force that connects one molecule to another. Think of it as a crucial handshake that helps molecules recognize each other and organize themselves. This type of bonding is important for creating complex and stable structures, especially in crystals.

Hydrogen bond forms between three key parts:

1.A donor (D) atom, like oxygen (O) or nitrogen (N), that is connected to a hydrogen (H) atom.
2.The hydrogen (H) atom itself.
3.An acceptor (A) atom, also like O or N, that has a lone pair of electrons.
The hydrogen atom gets a slight positive charge, which is attracted to the slight negative charge of the acceptor atom. This attraction is the hydrogen bond.28

Dipole-Dipole Interactions
These attractive forces occur between polar molecules. Polar molecules have a permanent dipole, meaning they have a slightly positive end (δ+) and a slightly negative end (δ−) due to an unequal sharing of electrons. The positive end of one polar molecule is attracted to the negative end of a neighboring polar molecule, creating a dipole-dipole interaction. These forces are stronger than London dispersion forces but weaker than hydrogen bonds. A classic example is the interaction between two hydrogen chloride (HCl) molecules.

London Dispersion Forces (LDF)
Also known as van der Waals forces. London dispersion forces are the weakest of all intermolecular forces and are present in all molecules, whether they are polar or nonpolar. These forces are caused by the temporary, random fluctuations of electrons in a molecule's electron cloud. At any given moment, the Electrons might be unevenly distributed, creating a temporary, or "instantaneous," dipole. This temporary dipole can then induce a similar, temporary dipole in a neighboring molecule, leading to a weak, fleeting attraction. The more electrons a molecule has, the more "polarizable" it is (meaning its electron cloud can be more easily distorted), and the stronger its London dispersion forces will be.27
The strength of London dispersion forces increases with the number of electrons in a molecule, which is why larger, heavier molecules have higher boiling points than smaller ones.29

Ion-Dipole Interactions
These are generally the strongest intermolecular forces. They occur when an ion (a charged atom or molecule) interacts with a polar molecule (a dipole). A good example is what happens when you dissolve table salt (NaCl) in water. The positive sodium ions (Na+) are attracted to the negative oxygen ends of the water molecules, and the negative chloride ions are attracted to the positive hydrogen ends of the water molecules.26

2.2 SUPRAMOLECULAR SYNTHON:
A supramolecular synthon is a term used in crystal engineering to describe a specific, recurring structural unit formed by non-covalent interactions between two or more molecules in a crystal.
It's essentially the building block or recognition feature that dictates how molecules arrange themselves to form a crystal structure.30
Focus: Using weak, non-covalent interactions (like hydrogen bonds, π-stacking, or van der Waals forces) to assemble molecules. Think of these like temporary, magnetic connections instead of permanent, welded ones.
The Process: Molecules with specific functional groups are designed to "recognize" and "attract" each other. When they come together, they self- assemble into larger, ordered structures like crystals or polymers.
The Advantage (Self-Correction): The weak interactions are reversible. If a molecule connects incorrectly, it can easily detach and try again until it finds the most stable (lowest energy) arrangement. This is called self- sorting or error correction, making the process naturally more efficient and precise.31

2.3 METHODS Of CRYSTAL ENGINEERING FOR ENHANCING SOLUBILITY AND BIOAVAILABILITY:

2.3.1 Co-crystlization
A co-crystal is a special type of solid material that is made up of two or more different molecules that are held together in a specific, fixed arrangement within a crystal lattice.
Crucially, the arrangement in the crystal lattice is not based on ionic bonds. The structure relies on noncovalent interactions between the active pharmaceutical ingredient (API) and a coformer. These noncovalent interactions include van der Waals forces, π-stacking,
Advantages:
Cocrystallization is a successful method to modify an API's physicochemical properties while keeping the API's structure intact.
Improved Properties: It can lead to better drug solubility, dissolution rate, bioavailability, permeability, physical and chemical stability, and even processing ability.
Manufacturing: It offers more flexibility in engineering solid form polymorphism, allowing

control over the stability and/or efficacy of the final product.

Cocrystallization Techniques:

• Solvent-based: The solvent-based techniques for cocrystallization involve dissolving the Active Pharmaceutical Ingredient (API) and the coformer in a suitable solvent to form a homogenous solution, followed by a process that induces crystallization of the new cocrystal phase.

• Solvent-free: The most prominent solvent-free techniques for cocrystallization rely on applying mechanical energy (grinding) or thermal energy (melting/extrusion) to bring the Active Pharmaceutical Ingredient (API) and the coformer into intimate contact, driving the formation of the new crystalline cocrystal structure.32

2.3.2 Co- crystal salt

A "cocrystal salt," also called a salt-cocrystal hybrid or ionic cocrystal, is a multicomponent crystal that is structurally ambiguous or intentionally contains both ionic and non-ionic interactions.

Partial Proton Transfer: This form typically occurs when the ΔpKa Between the drug and the Coformer/counter-ion is in an intermediate or "gray area" (e.g., between 1 and 3), leading to incomplete or partial proton transfer.

Dual Interaction: The crystal structure contains both the ionic bonds characteristic of a salt and the non-ionic hydrogen bonding/van der Waals forces characteristic of a cocrystal. Complex Stoichiometry: It may involve a complex ratio where one component exists in both its neutral (cocrystal-like) and ionized (salt-like) forms within the same lattice.

Importance:

Salts and cocrystals to improve drug properties like solubility, dissolution rate, and stability. The cocrystal salt is simply a result of exploring the full range of solid forms, offering a way to fine-tune physicochemical properties when a pure salt or a pure cocrystal doesn't provide the optimal balance of properties.33

2.3.3 Solid dispersion

Solid dispersion is defined as the dispersion of one or more active ingredients (usually hydrophobic, or water-hating) in an inert carrier (usually hydrophilic, or water-loving) at the solid state. This is usually done to make the drug dissolve faster when a person takes it, or sometimes, as this paper focuses on, to control its release.

The drug and the solid material are mixed together, either by melting them, dissolving them in a solvent (a liquid that evaporates), or by grinding them up really well.

When a solid dispersion is made, the drug often changes its form, which affects how it dissolves. Sometimes, the drug is fully dissolved in the solid material; sometimes, it's just very tiny particles spread throughout.24

There are two major methods of preparing solid Dispersion:

1.melting method

Melt the Mixture: You mix the drug and the chosen carrier substance (the material that holds the drug) and heat the whole thing up until it melts completely.

Mix Thoroughly: This creates a liquid mixture where the drug is dissolved or perfectly dispersed within the molten carrier.

Cool and Pulverize: This liquid mixture is then allowed to cool down, causing it to solidify. Once Solid, it's ground up (pulverized) into a fine powder that can be used to make tablets or capsules.

Challenges and Improvements:

Drug Degradation: Because you use high temperatures to melt the mixture, there's a risk of the drug breaking down or becoming less effective (degradation).

Poor Mixing: Sometimes the drug and the carrier don't mix perfectly well, which leads to an incomplete or poor dispersion.

2.Solvent Evaporation Method

Dissolve Drug and Carrier: Both the drug and the carrier material are dissolved together in a common, volatile solvent (a liquid that evaporates easily, like alcohol). This creates a clear solution.

Evaporate the Solvent: The liquid solution is then spread out, and the solvent is removed (evaporated) by using a vacuum or simply letting it air-dry.

Solid Product: As the solvent disappears, the drug and carrier are left behind as a solid residue—the solid dispersion.

Challenges and Improvements:

Avoids High Heat: Since the drug is dissolved in a solvent, you don't need to heat it to a high temperature. This means the drug is much less likely to degrade.35

2.3.4 Amorphous forme

An amorphous solid (like glass or certain plastics) is essentially a solid drug (API – Active Pharmaceutical Ingredient) where the molecules don't have a neat,

repeating, long-range arrangement in three dimensions. Think of them as molecules frozen randomly, much like they would be in a very thick liquid. This is why it's also called a glassy state or a super-cooled liquid.

The amorphous form is important in medicine because it generally has:

Better Solubility: It dissolves more easily.

Higher Vapour Pressure: It tends to evaporate more readily.

Is because the amorphous form has higher internal energy (more stored energy) and higher specific volume (takes up more space per unit mass) compared to its perfectly ordered twin, the crystalline form. The extra energy makes it easier for the substance to transition into a solution.

Crystalline Solid (Ordered) When a crystalline solid is heated, its internal properties like Enthalpy (H) (total energy) and Specific Volume (V) (space it takes up) change very little. This is because crystalline solids are very stable. At the melting temperature ™, there is a sudden, sharp jump (discontinuity) in both H and V. This jump marks the first-order phase transition—the moment it melts into a liquid.

Cooling the Melt If this liquid is cooled slowly, the molecules have time to find their places and will re-form the perfectly ordered crystalline solid.

If the liquid is cooled very quickly (or if the substance has certain properties), the molecules don't have time to order themselves, and they "freeze" in place randomly, forming the amorphous (glassy) solid.

Why the Amorphous Form is Tricky (and Important)

• The Glassy State and Instability:

When a liquid melt is cooled slowly, its molecules naturally arrange themselves and turn back into the stable, crystalline solid.

Glass Transition Temperature (TG): This is the specific temperature where the super-cooled liquid turns into this stiff, non-liquid glass.

It has better properties for drugs, like:

Higher Solubility: It dissolves faster in the body.

Higher Vapour Pressure: It transitions into a gas more easily.36

• Stabilizing Amorphous Drugs

Stabilizing this high-energy amorphous state—preventing it from changing back into the crystal form—is a major challenge when creating drug products. It's crucial for two reasons:

Maintaining Solubility: If the drug turns crystalline, it won't dissolve as well, making the medicine less effective.

Shelf Life: The stability of the drug's solid form directly impacts the shelf life (how long the medicine lasts) and its overall effectiveness (potency).37

Solubility Advantage of Amorphous Form:

The amorphous form of a drug (API) is preferred because it dissolves much better (has higher apparent solubility) than its stable, ordered crystalline form.

Higher Internal Energy: The amorphous form has extra energy stored in its random structure, making it easier to break apart and dissolve.

Increased Surface Area: Because the molecules don't have a neat, long-range order, the powder particles are Often rougher and have more surface area exposed to the solvent (like water).

Higher Mobility: The molecules in the amorphous form are not tightly locked in place. They are more mobile, which helps them leave the solid structure and go into the solution.38

2.3.5 polymorphism

Polymorphism is the phenomenon where a compound can crystallize into more than one crystal structure (called polymorphs), even though the chemical composition is the same.

Origin: Polymorphs arise from different arrangements or conformations of molecules in the crystal lattice. Different polymorphs possess different crystal packing and/or different molecular conformations.

Significance: Polymorphism is of fundamental and practical importance, particularly in the pharmaceutical industry and agrochemicals, because different polymorphs have distinct physical and chemical properties. These properties include solubility, dissolution rate, bioavailability, and stability, which are critical for drug efficacy and shelf life.25

1 .Monotropy

This type of polymorphism occurs when one form is stable and the other is metastable across the entire temperature range, and the change from the metastable to the stable form is not reversible.

Key Characteristics:

No transition temperature exists where the stability of the forms switches.

The metastable form will eventually convert to the stable form, but the reverse doesn't happen spontaneously.

Example: Diamond and Graphite. Graphite is the only stable solid allotrope of carbon; diamond is metastable and very slowly changes into graphite at all temperatures. Niccerogoline's orthorhombic and triclinic forms are also given as an example.

2. Dynamic Allotropy

This type is characterized by various forms coexisting in equilibrium over a range of temperatures, with the proportion of each form varying with temperature (and sometimes pressure). The separate forms may have different formulas.

Key Characteristics:

The forms coexist in equilibrium.

The equilibrium proportion changes with temperature.

It resembles enantiotropy but involves forms that may be structurally distinct in the liquid state or have different formulas.

Example: The two liquid forms of sulfur (λ-sulfur and μ-sulfur). As liquid sulfur is heated above its melting point, λ-sulfur converts to μ-sulfur, causing changes in colour (from amber to darker) and viscosity (reaching a maximum around 180C°).

3.Enantiotropy

This occurs when one form is stable below a specific transition temperature, and the other form is stable above that temperature. The transition is reversible.

Key Characteristics:

There is a definite transition temperature (or transition point).

The stability of the two forms reverses across this point.

The change from one form to the other is reversible.

Example: Rhombic sulfur and Monoclinic sulfur. Rhombic sulfur is stable below 95.5C°.

Monoclinic sulfur is stable between 95.5C° and its melting point (119.25C°

The change from one crystalline form to the other is reversible at the transition point (95.5C°).39

2.4 CHARACTERIZATION TECHNIQUES FOR CRYSTAL ENGINEERING:

2.4.1 X-ray Diffraction (XRD)

X-ray Diffraction (XRD) is based on the interaction of X-rays with the electrons of atoms in a solid material.

Scattering and Interference: When X-rays strike a solid, they are scattered by the electrons. These scattered waves then interfere with one another.

Diffraction: Diffraction is defined as the constructive interference of these scattered X-rays.

Periodicity is Key: Constructive interference (diffraction) occurs because of the orderly arrangement (periodicity) of atomic structures in crystalline solids.

Applications of XRD

XRD is a powerful technique used for several material characterization purposes:

Phase Identification/Mineral Analysis: XRD enables the identification of several minerals or phases present in a sample.

Assessment of Crystallinity: It is used for estimating the treatment effects on the crystallinity of materials.

For example, a study used XRD to show that combustion treatment enhanced a material's crystallinity to a greater extent than chemical oxidation.

Structural Analysis: By analyzing peak positions and intensities, one can determine atomic positions, and the size and shape of the unit cell.40

Powder X-Ray Diffraction (PXRD):

PXRD is an analytical technique used for the structural characterization of crystalline solids (polycrystalline materials). It relies on the elastic scattering of monochromatic X-rays (λ) from the periodically ordered atomic planes in a sample.

PXRD, particularly for determining crystal structures that cannot be solved using traditional single-crystal methods.

Purpose and Necessity of Powder X-Ray Diffraction

PXRD is essential for determining the crystal structure of material

III. FUTURE AND PRESPECTIVE

3.1 Role Of Crystal Engineering In Pharmaceutical Science

Crystal engineering is the design and growth of crystalline molecular solids with the goal of impacting material properties. Its principal tool is the hydrogen bond, which directs the majority of intermolecular interactions in molecular solids.49

That exploring the above concepts (crystallization, packing, interaction, and recognition) is intended to provide an 'understanding of crystal engineering approaches as a means of Addressing the challenges of low aqueous solubility'. This suggests that by rationally controlling the solid-state structure of drug molecules, crystal engineering can be used to improve

the physicochemical properties of drugs, such as their solubility, which is a major hurdle in formulation.1

3.2 Future Challenges and Prospects

Understanding Requirements: Determining the required material structure and properties for a specific compound based on its intended use.

Creative Integration: Integrating crystal engineering principles within the constraints of pharmaceutical acceptability to create new forms of active ingredients with desirable properties for formulation and delivery.

Facilitating Advances:

Learning and progress in crystal form design will be significantly facilitated by advancements in:

Automation: New techniques in crystallization automation.

Spectroscopy & Microscopy: Improved analytical techniques, including:

- Raman and IR microscopy
- Terahertz spectroscopy
- Atomic Force Microscopy (AFM)

Instrumentation: Increasingly sophisticated X-ray diffraction lab instrumentation. Data Mining: Further enhancements in tools associated with the Cambridge Structural Database (CSD), leveraging the growing number of high-quality crystal structures to generate new knowledge about molecular interactions.49

The complex behaviour of intermolecular interactions. The unpredictable effects of remote functional groups (known as interaction interference).50

Hydrogen bonding continues to evolve, and the importance of weaker interactions remains a point of challenge. Controlling the Crystallization Process: The "crystallization reaction" is subject to phenomena that are difficult to reproduce, including polymorphism (different crystal forms of the same compound), hydration, solvation, and the formation of co-crystals.

Early Stage of Functional Engineering: The goal of precisely designing a solid with desired physical and chemical properties (functional engineering) is considered to be "still in its infancy" despite progress in structural design Focus on Functional Engineering: There is a growing convergence between structural engineering (designing based on building blocks) and functional engineering (targeting collective crystal properties), motivating in-depth studies into the functionality of crystalline solids.2

Crystal engineering offers a wide range of opportunities for optimizing drug performance, Particularly through multicomponent crystalline systems like cocrystals.

Systematic Property Tuning: CE allows for the modification of multiple physicochemical properties of an API, including solubility, dissolution rate, physical/chemical stability, melting point, hygroscopicity, and mechanical properties, without altering the molecule's fundamental structure.

Nanomaterials: The development of Nano Co-crystals (NCC) is highly promising. Nano-scaling, often combined with cocrystallization, provides a massive increase in surface area, which leads to greatly enhanced dissolution rates and superior bioavailability compared to conventional forms.

Targeted Delivery: Recent advances show the potential for using crystal engineering to achieve more sophisticated systems, such as targeted drug delivery for novel molecules like anticancer drugs, antimicrobials, and vaccines.51

Functional Materials Synthesis: Beyond solubility, crystal engineering holds promise for developing functional materials, such as porous frameworks (like Metal-Organic Frameworks or MOFs), that could be Used for highly selective drug delivery or as platforms for solid-state reactions.

Rational Design and Multi-Component Solids: The field is actively shifting towards a fully design-based approach, focusing on the engineering of multi-component solids like pharmaceutical co-crystals and salts. These supramolecular solid forms allow for simultaneous modification of multiple properties (solubility, melting point, and stability) by pairing the API with a safe co-former.

Lack of Reliable Crystal Structure Prediction (CSP): The biggest hurdle is the inability to reliably predict the most stable crystal structure, or polymorph, of a molecule solely from its chemical structure. Although computational methods are improving, the sheer number of possible packing arrangements makes de novo prediction a significant challenge.52

IV. CONCLUSION

Crystal engineering has emerged as a powerful strategy in pharmaceutical sciences to overcome the challenges of poor solubility and. Low bioavailability of active pharmaceutical ingredients (APIs). By

manipulating crystal forms at the microscopic scale through approaches such as cocrystallization, salt formation, solid dispersions, polymorphism, and amorphization, researchers can significantly improve the dissolution rate, stability, and therapeutic efficacy of drugs without altering their chemical structure. These techniques not only enhance pharmacokinetic performance but also expand formulation possibilities for poorly soluble compounds. Moreover, advanced characterization tools like PXRD, SEM, DSC, Raman spectroscopy, and ss-NMR provide critical insights into solid-state properties, ensuring the reliability and stability of engineered crystals. The integration of nanotechnology, such as nano-cocrystals, further holds promise for maximizing drug absorption and enabling targeted delivery systems. While crystal engineering offers immense potential, challenges remain in reproducibility, long-term stability of amorphous forms, and reliable prediction of polymorphic outcomes. Future perspectives suggest a shift toward rational design and functional engineering, supported by advancements in automation, computational modeling, and structural Databases. Crystal engineering represents a vital frontier in modern pharmaceutics, providing innovative solutions to enhance solubility, bioavailability, and overall drug performance paving the way for more effective, safe, and economical therapeutic options.

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