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A review on Pharmaceutical cocrystal: coformer selection, method of preparation, characteristics of cocrystal and its regulatory aspects

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ABSTRACT

Pharmaceutical co-crystals are a novel class of pharmaceutical materials with a potential for improving their polished physical characteristics to produce stable, patentable solid forms. These complex crystalline forms have an impact on relevant physicochemical factors such as the rate of dissolution, chemical stability, physical stability, and so forth that in ultimately produce materials with better qualities than the free medication. Nonetheless, coformer selection is crucial for enhancing the cocrystallization-derived API properties. Choosing the right coformers enhances the drug's physicochemical characteristics, therapeutic efficacy, and minimizes side effects. Different method can be used for the selection of coformer and the preparation of cocrystal which contain solvent evaporation, Neat grinding, Solvent grinding, antisolvent method etc. This review concluded with brief discussion of pharmaceutical consideration and regulatory guidelines for the cocrystal.

INTRODUCTION

The optimization of properties such as solubility, dissolution rate, mechanical properties, hygroscopicity, physical stability, and chemical stability is of strategic importance when determining the physical form in which active pharmaceutical ingredients (APIs) will be administered. Since crystalline APIs tend to be more stable, reproducible in their properties, and easier to isolate in high purity than amorphous drugs, most APIs are solid, crystalline, and exist in crystal form.[1]In spite of this, 40 percent of commercial compounds and drugs under development and 80% of drug substances in production have solubility issues.[2]Biopharmaceutical classification system (BCS) class II drugs have low solubility and are limited in their oral absorption. Thus, poor solubility is one of the most common issues hindering drug development [3]

The arrangement of atoms in the crystal lattice and unit cell directly affects the properties of crystalline materials. As a result, tailoring the crystal packing arrangement can modify the physicochemical properties of solid drug forms.[4, 5] It is hard to define a co-crystal exactly, but it can be defined as a crystalline compound containing two or more neutral molecules in a definite stoichiometric ratio. A co-crystal differs from a salt crystal due to the arrangement of cationic and anionic components in salt crystals. Pharmaceutical co-crystals comprise one or more secondary components known as crystal co-formers in addition to at least one API (active pharmaceutical ingredient). An organic substance, such as a carboxylic acid, an amino acid, alcohol, or sugar, is the co-former.[6]When it comes to pharmaceutical cocrystals, coformers are materials that the FDA has classified as GRAS (Generally Recognized As Safe), or safe substances to eat.[7] Cocrystals are described as "homogenous (single phase) crystalline structures made up of two or more components in a single structure" by the European Medicines Agency (EMA).specific stoichiometric ratio at which the crystal's arrangement .Unlike with salts, the lattice is not based on ionic bonds. In contrast to According to the FDA and EMA's definition, cocrystals are an effective substitute for the same API salts.[8] Stated differently, theCocrystal and API are thought to be equivalent, but cocrystal displays unique characteristics of pharmacokinetics.[9]

In this review, we will summarize the recent advances of pharmaceutical cocrystals, including selection of conformer, chemistry of cocrystal formation, preparation methods, characterization, challenges, and application of cocrystal.

2.Methods used for selection of coformer:

As was previously mentioned, coformers are crucial to the development of cocrystals. When forming cocrystals with a specific coformer, variables like the kind of functional group, pKa, their molecular size, and their physical form must be taken into account.[10] The knowledge-based approach and the experimental method are the main methods used to choose the coformers. Trial and error is the foundation of the experimental approach. A variety of factors are used to select suitable coformers, including hydrogen bonding, pKa-based models, supramolecularsynthon compatibility using the Cambridge Structure Database (CSD), lattice energy calculation, Hansen solubility parameter, thermal analysis, saturation temperature measurements, virtual cocrystal screening (using molecular electrostatic potential surfaces-MEPS), etc.[11][12]. Because of the structural characteristics of the coformer and API, the knowledge-based approaches can therefore predict the formation of cocrystals even before experiments are conducted. The structural components of supermolecules that can result from intermolecular interactions are known as supramolecular synthons.Two categories of supramolecularsynthons exist: homosynthonssupramoleculars possessing similar supramolecularheterosynthons with distinct but complementary functions and self-complementary features. Heterosynthons are usually more resilient. Generally speaking, carboxylic acid heterosynthons and amide homodimers are preferred [13, 14].

Cambridge Structural Database (CSD):

Crystallographic data about the hydrogen bonds that are formed between the drug and the coformer is contained in the CSD. There are currently more than 1.2 million crystals in the CSD repository frameworks [15, 16]

Hydrogen-Bond Rules:

The hydrogen-bond rule represents an additional method for choosing a coformer. An attractive interaction between an electronega-tive atom (X) and a hydrogen atom is known as the hydrogen bond (X-H). A molecule can form a hydrogen bond with another molecule or with itself [17]. For a particular functional group or combination of functional groups in which hydrogen bonds are formed, the hydrogen bond rule offers useful information about the favored hydrogen-bond selectivity, connectivity patterns, and stereo-electronic properties of hydrogen bonds. In general, the formation of hydrogen bonds follows three rules.Donohue proposed the first rule, which states that hydrogen bonds will be formed using all of the available acidic hydrogen in a compound's molecular crystal structure.[18]

pKa Rule:

The BCS Class II medications are categorized into three groups according to their pH-dependent solubility: Iia (acidic drugs), Iib (basic drugs), and Iic (neutral drugs). Medications categorized as weakly acidic ($pKa \leq 5$) have a greater water solubility at the intestinal pH of alkalinity. In contrast, weakly basic drugs ($pKa \geq 6$) are categorized as class basic drugs because they have a higher aqueous solubility at the acidic pH of the stomach. Neutral drugs are those that do not show apH-dependent solubility.[19][20]. A study of proton transfer can predict the formation of cocrystal and salt, and this can be found using the formula $\Delta pKa = [pKa\ (base) - pKa\ (acid)]$. Proton transfer between acid and base is indicated by a pKa value difference of more than two or three between the API and coformer. Cocrystal formation is indicated by a smaller pKa value difference (less than 0), whereas a large A variation in pKa values (≥ 2 or 3) signifies the formation of salt [21]

Method of Preparation of Cocrystal:

The cocrystallization of an API by a supersaturated solution in the presence of a coformer is the most widely used technique for the large-scale industrial production of cocrystals. Most of the time, an undersaturated mixture is slowly cooled until the dissolution limit is reached, resulting in about 40% supersaturation. In addition, the amount of the coformer (reaction cocrystallization) can be adjusted to induce solution mediated phase transitions (SMPT).[1]

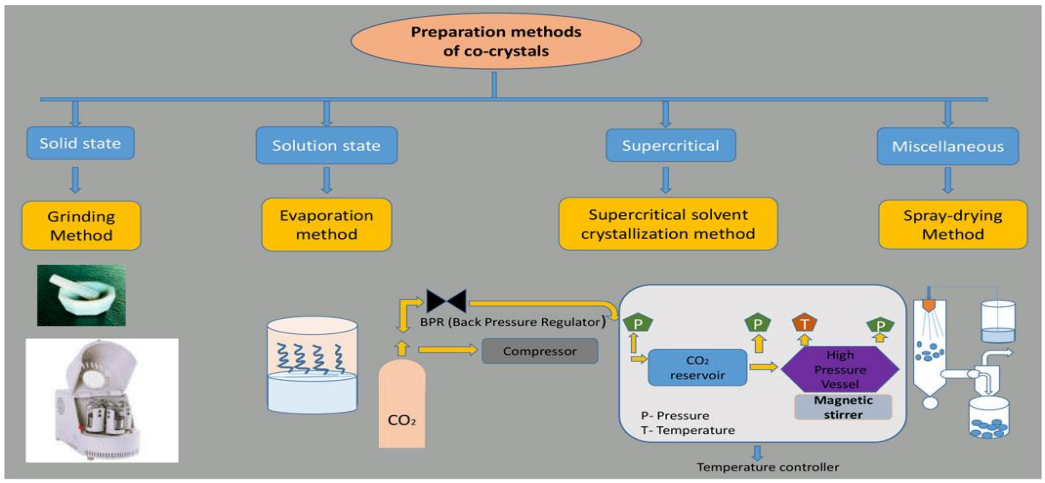

Figure 1. Different method of co crystal Preparation

Solvent Evaporation Method:
This method is the most widely applied one for producing cocrystals. In a common solvent with an appropriate stoichiometric ratio, the materials (API and coformer) are dissolved until they entirely evaporate[22]. A thermodynamically preferred product is produced during evaporation when the molecules' solution changes due to the formation of hydrogen bonds between various functional groups. The choice of solvent has a significant impact on solubility. The component with the lower solubility will precipitate if the two components have different solubilities. Solvent evaporation is a small-scale method of preparing cocrystals that produces high-quality, pure crystals without the need for complicated equipment. However, there are two drawbacks: it requires a lot of solvent, and its scalability is restricted.[1, 23]

Neat grinding method:
This process of cocrystallization doesn't use a solvent. The cocrystal is produced by admixing the appropriate stoichiometric amounts of solid materials, pressing and crushing them together using a mortar and pestle, ball mill, or vibrator mill. The typical grinding time is between thirty and sixty minutes. This technique can be used to prepare a large number of cocrystals, and any failure is usually the result of using the incorrect settings.[1]

Solvent grinding method:
This is a modification of neat grinding that has been used to improve supramolecular selectivity in crystalline systems, both polymorphic and stoichiometric, by incorporating a small amount of solvent into the grinding process[24]. A very tiny amount of solvent (~a few tenths of an equivalent amount of solvent per mole of the component) is added after the two components have been mixed. Given that the solvent's tiny quantity does not contribute to the finished product, its action can be characterized as catalytic. Its benefits include better product crystallinity, enhanced performance, and controllability over polymorph production. Moreover, a wide range of coformers can be used for cocrystallization. Liquid-assisting grinding has several drawbacks, such as being a small-scale process with high energy consumption and poor product purity performance. Pterostilbene-carbamazepine cocrystals were patented using liquid-assisted grinding .

Slurring technique:
The addition of the crystallization solvent is a straightforward procedure [25]. After the coformer is added to the solution created by the solid API dissolving in the solvent, the suspension is agitated, filtered, and dried.

Antisolventcocrystallization:
To encourage the precipitation of the solids, a solvent that is less soluble in the compound is frequently added to the solution. After filtering the resultant suspension, XRPD can be used to characterize the collected solid. This method's drawbacks include its poorer performance in comparison to solvent-based grinding and the substantial amount of solvent required.[1]

Use of supercritical fluids:
Supercritical fluid (SCF) is an excellent solvent that can replace organic solvents due to its exceptional ability to dissolve materials like a liquid and diffuse through solids like a gas (gas flow properties and dissolving liquid properties). The most popular supercritical fluid for cocrystallization is CO2; it can be used as a solvent, an anti-solvent, or an atomized anti-solvent [26]. It include cocrystallization with supercritical solvent, supercritical antisolvent, atomized antisolvent.[1]

Characterization of Cocrystals:
A variety of techniques have been used to clarify intermolecular interactions and characterize pharmaceutical cocrystals.The methods for characterizing cocrystals, particularly those that are frequently employed in drug delivery and development laboratories, are briefly covered in the final section of this review.

Single-crystal and powder X-ray diffraction (XRD): XR
The most common tool for characterizing cocrystals is a combination of methods. Since cocrystals have distinctive sharp peaks that differ from the peaks of the cocrystal components, single-crystal XRD is frequently used for the structure solution of cocrystals, whereas powder XRD (PXRD) is primarily used for identification purposes.[1]

Thermal analysis:
The term "thermal analysis" refers to a set of methods that record changes in the physical or chemical properties of a sample's thermal properties through time-controlled temperature changes (heating, cooling, alternating, or maintaining at a constant temperature) in a controlled atmosphere. The measured properties that can be recorded include mass, heat or heat flow, enthalpy, and so on. The most applicable methods for characterizing cocrystals are thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and differential scanning calorimetry (DSC), along with hot-stage microscopy (HSM). The following provides a brief overview of the methods used for cocrystal characterization.

Differential Scanning Calorimetry (DSC):
In the pharmaceutical industry, differential scanning calorimetry, or DSC, is frequently employed to characterize co-crystals. Utilizing this method, the co-crystal and pure components heat up gradually under control. The obtained thermogram is examined carefully to ensure the potential for co-crystal development. In this manner, eutectic melt produced when heating slowly Re-forms crystals melts after reaching the co-crystal form, regardless of the drug to coformer ratio. Since it enables co-crystal detection, the thermogram produced by the DSC scan is used for co-crystal screening. In contrast to the pure thermogram of drug and coformer, the thermogram of co-crystals displays an exothermic peak that is followed by an endothermic peak. Co-crystals will exhibit distinct melting points and heats of fusion when compared to their pure component counterparts. A thermogram of a physical mixture that is incapable of forming co-crystals will only show one endothermic peak connected to eutectic melting.[27]

Spectroscopy – vibrational, nuclear magnetic resonance:
The energy absorbed or scattered by the co-crystals' chemical bonds will differ from that of the pure components in vibrational spectroscopy (Raman and infrared), which helps to identify the co-crystals' structural behavior. Because of the hydrogen bonding that occurs between them, cocrystals display a different spectrum of bands in infrared spectroscopy than the pure drug and coformer. The bands of functional groups that have experienced hydrogen bonding clearly differ from one another. Because solid-state nuclear magnetic resonance can provide structural information about cocrystals, it is frequently used to characterize pharmaceutical ccrystals. Since this technique can determine the degree of proton, it is also used to differentiate between salts and cocrystals transfer. One of this method's primary drawbacks is the instrument's low sensitivity.[27]

Field emission scanning electron microscopy (FESEM):
To investigate the surface morphology of co-crystals, topography or FESEM are utilized. For the comparison, micrographs of the constituents and co-crystals from the FESEM investigations are used. Heat energy is not used in the field emission electron microscope; instead, a "cold" source is used. The electrons are released from the conductor's surface using a strong electric field. The cathode is made of a tungsten filament with a needle that is both thin and sharp (tip diameter 10-100 nm). A scanning electron microscope is attached to the field emission source in order to take co-crystal micrographs.[27]

Physical Properties modified by co crystal:
Melting Point:
A thermodynamic process where the free transition energy is zero, the melting point is a fundamental physical property that is defined as the temperature at which the solid and liquid phases are in equilibrium. While low m.p. may impede processing, drying, and stability, high m.p. is generally preferred but can also lead to low solubility (S) and hinder some molding processes. Because of their capacity to identify supplementary thermal data, differential scanning calorimetry (DSC) and the Kofler method are regarded as the preferred techniques for obtaining melting point data. A compound's purity can be determined and its classification can be made by finding its melting point**.**

Mechanical Properties:
In the production of solid dosage forms, the mechanical characteristics of crystalline materials play a crucial role in the processes of blending, milling, granulating, tableting, and coating. Elastic, plastic, viscoelastic, and fragmentation are the

mechanical deformation mechanisms for solid materials.Better plasticity qualities typically translate into superior compressibility, which is permanent and irreversible once stress is removed. For organic materials, good tableting behavior predicts greater plastic deformation and less elastic recovery. Slip plane-containing crystal structures would facilitate plastic deformation and ultimately enhance the behavior of bulk compaction.[28]

Bioavailability :
The term "bioavailability" describes the percentage of a medication that enters the bloodstream. Low bioavailability was a major reason for the preclinical failure of many drug candidates during the drug development process. Over the past ten years, cocrystallization has demonstrated its ability to enhance in vivo performance by increasing the solubility and bioavailability of drugs that are poorly soluble in water.[29]

Solubility:
A poorly soluble drug's solubility or rate of dissolution may be improved or decreased by cocrystallization[28]. Acyclovir l-tartaric acid, for instance, is more soluble than acyclovir 21's hydrate and amorphous forms. The melamine and cyanuric acid 1:1 cocrystal is a special illustration of the decreased solubility caused by cocrystallization. Because solubility and dissolution go hand in hand, if cocrystal solubility rises relative to API, intrinsic dissolution for cocrystals rises relative to pure drug, and vice versa. Co-crystal of ionized medication pH of the solution is the primary determinant of co-crystal solubility. This can be predicted using calculations based on the cocrystals' dissociation and degree of ionization equilibria[30, 31]

Pharmaceutical Considerations:
Co-crystals can enhance medications in a number of ways. These characteristics ought to be examined for every drug candidate to make sure that the advantages (much) outweigh any potential drawbacks of the novel dosage form. First off, one crucial factor is a drug's stability. It is necessary to take into account a number of stability factors, including moisture, chemical structure, air sensitivity, and the impact of acids and bases. These will affect the drug's effectiveness in the body as well as its shelf life. The drug may be exposed to a variety of environments. For example, the mouth's pH should always be higher than 5.5[32], whereas the stomach's gastric acid has a pH range of 1.5 to 3.5[32], The co-crystal frequently dissolves, and precipitation of a less soluble compound is possible. Adding surfactants to the medication could be one way to stop the medication from unintentionally re-crystallizing. Another crucial consideration in processing, packing, and storage is sensitivity to moisture. Moisture may cause the API to undergo undesired phase changes.[33]

Regulatory Guidelines for Pharmaceutical Cocrystals:
Guidelines for pharmaceutical cocrystals have been released by the European Medicines Agency (EMA) and the US Food and Drug Administration (USFDA). Pharmaceutical cocrystals are regarded by the USFDA as novel crystalline solid forms that improve the stability, bioavailability, and processability characteristics of APIs. The elements that make up the crystalline lattice of pharmaceutical cocrystals should interact nonionically, which sets them apart from salts. Cocrystals and solvates are closely related, but in pure form, at room temperature, the conformer is not a liquid.

The ΔpKa rule, which states that for the formation of a cocrystal, the difference between the pKa values of the cocrystal components should be less than 0, or any analytical evidence can be used by the applicant to demonstrate that the interaction between the API and conformer is nonionic. Additionally, the applicant must demonstrate that the API and conformer dissociate before reaching the site of action for pharmacological activity through in vitro dissolution and/or solubility studies. Regulation-wise, cocrystals of an API are viewed as distinct variations of the same API rather than as a brand-new API. Drug-drug cocrystals are regarded as fixed-dose combination products rather than as a novel single API, whether they contain an inactive conformer or not.[34]

CONCLUSION

The main causes of an active pharmaceutical ingredient's (API) failure in the current situation are poor permeability, low bioavailability, poor solubility, poor dissolution rate, and instability. The researchers' main goal is to mitigate these problems with APIs. Cocrystallization is a tried-and-true method for improving the physicochemical characteristics of APIs and resolving their associated issues. Because the final properties of the cocrystal depend on the coformer's characteristics and how it interacts with the API, coformers are essential to the cocrystallization process. Studies that show how the cocrystallization trials improved the previously listed API properties have been presented. In summary, this review offers a thorough explanation and examples of the physicochemical characteristics, preparation techniques, and range of uses for cocrystals. The cutting-edge technologies comprehensive regulatory guidance will also progress the translational research on drug cocrystal development for applications in healthcare. More medication products based on crystals are thought to be offered commercially to patients in the future.

REFERENCES

[1]. Karagianni, A., M. Malamatari, and K. Kachrimanis, *Pharmaceutical cocrystals: New solid phase modification approaches for the formulation of APIs.* Pharmaceutics, 2018. **10**(1): p. 18.

[2]. Loftsson, T. and M.E. Brewster, *Pharmaceutical applications of cyclodextrins: basic science and product development.* Journal of pharmacy and pharmacology, 2010. **62**(11): p. 1607-1621.

[3]. Lipinski, C.A., et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.* Advanced drug delivery reviews, 1997. **23**(1-3): p. 3-25.

[4]. Schultheiss, N. and A. Newman, *Pharmaceutical cocrystals and their physicochemical properties.* Crystal growth and design, 2009. **9**(6): p. 2950-2967.

[5]. Datta, S. and D.J. Grant, *Crystal structures of drugs: advances in determination, prediction and engineering.* Nature Reviews Drug Discovery, 2004. **3**(1): p. 42-57.

[6]. Wouters, J. and L. Quéré, *Pharmaceutical salts and co-crystals*. 2011: Royal Society of Chemistry.

[7]. Roberts, A. and L.A. Haighton, *A hard look at FDA's review of GRAS notices.* Regulatory Toxicology and Pharmacology, 2016. **79**: p. S124-S128.

[8]. Agency, E.M., *Reflection paper on the use of cocrystals of active substances in medicinal products*. 2015, European Medicines Agency Amsterdam, The Netherlands.

[9]. Kavanagh, O.N., et al., *Pharmaceutical cocrystals: from serendipity to design to application.* Drug Discovery Today, 2019. **24**(3): p. 796-804.

[10]. Manin, A.N., et al., *Hydrogen bond donor/acceptor ratios of the coformers: Do they really matter for the prediction of molecular packing in cocrystals? The case of benzamide derivatives with dicarboxylic acids.* Crystal Growth & Design, 2018. **18**(9): p. 5254-5269.

[11]. Kumar, S. and A. Nanda, *Pharmaceutical Cocrystals: An Overview.* Indian Journal of Pharmaceutical Sciences, 2017. **79**(6).

[12]. Surov, A.O., et al., *Virtual Screening, Structural Analysis, and Formation Thermodynamics of Carbamazepine Cocrystals.* Pharmaceutics, 2023. **15**(3): p. 836.

[13]. Vishweshwar, P., et al., *Pharmaceutical co-crystals.* Journal of pharmaceutical sciences, 2006. **95**(3): p. 499-516.

[14]. Kuminek, G., et al., *Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5.* Advanced drug delivery reviews, 2016. **101**: p. 143-166.

[15]. Singh, M., et al., *Cocrystals by Design: A Rational Coformer Selection Approach for Tackling the API Problems.* Pharmaceutics, 2023. **15**(4): p. 1161.

[16]. Thakuria, R., B. Sarma, and A. Nangia, *7.03—Hydrogen bonding in molecular crystals.* Comprehensive supramolecular chemistry II. Elsevier, Oxford, 2017: p. 25-48.

[17]. Arunan, E., et al., *Definition of the hydrogen bond (IUPAC Recommendations 2011).* Pure and applied chemistry, 2011. **83**(8): p. 1637-1641.

[18]. Etter, M.C., *Hydrogen bonds as design elements in organic chemistry.* The Journal of Physical Chemistry, 1991. **95**(12): p. 4601-4610.

[19]. Goswami, P.K., R. Thaimattam, and A. Ramanan, *Crystal engineering of multicomponent crystal forms of p-aminosalicylic acid with pyridine based coformers.* Crystal Growth & Design, 2016. **16**(3): p. 1268-1281.

[20]. Fei, T., et al., *Design and synthesis of a series of CL-20 cocrystals: six-membered symmetrical N-heterocyclic compounds as effective coformers.* Crystal Growth & Design, 2019. **19**(5): p. 2779-2784.

[21]. Childs, S.L., G.P. Stahly, and A. Park, *The salt− cocrystal continuum: the influence of crystal structure on ionization state.* Molecular pharmaceutics, 2007. **4**(3): p. 323-338.

[22]. Weyna, D.R., et al., *Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: mechanochemistry vs slow evaporation from solution.* Crystal Growth and Design, 2009. **9**(2): p. 1106-1123.

[23]. Childs, S., *Novel Cocrystallization of Hydrochloric Acid Salt of an Active Agent.* Can. Patent CA2514092 A, 2004. **1**: p. 5.

[24]. Jones, W., W.S. Motherwell, and A.V. Trask, *Pharmaceutical cocrystals: An emerging approach to physical property enhancement.* MRS bulletin, 2006. **31**(11): p. 875-879.

[25]. Takata, N., et al., *Cocrystal screening of stanolone and mestanolone using slurry crystallization.* Crystal Growth and Design, 2008. **8**(8): p. 3032-3037.

[26]. Padrela, L., et al., *Formation of indomethacin–saccharin cocrystals using supercritical fluid technology.* European Journal of Pharmaceutical Sciences, 2009. **38**(1): p. 9-17.

[27]. Thayyil, A.R., et al., *Pharmaceutical co-crystallization: Regulatory aspects, design, characterization, and applications.* Advanced Pharmaceutical Bulletin, 2020. **10**(2): p. 203.

[28]. Guo, M., et al., *Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications.* Acta Pharmaceutica Sinica B, 2021. **11**(8): p. 2537-2564.

[29]. Childs, S.L., P. Kandi, and S.R. Lingireddy, *Formulation of a danazol cocrystal with controlled supersaturation plays an essential role in improving bioavailability.* Molecular pharmaceutics, 2013. **10**(8): p. 3112-3127.
[30]. Aakeröy, C.B., S. Forbes, and J. Desper, *Using cocrystals to systematically modulate aqueous solubility and melting behavior of an anticancer drug.* Journal of the American Chemical Society, 2009. **131**(47): p. 17048-17049.
[31]. Masuda, T., et al., *Cocrystallization and amorphization induced by drug–excipient interaction improves the physical properties of acyclovir.* International journal of pharmaceutics, 2012. **422**(1-2): p. 160-169.
[32]. Rekdal, M., et al., *Applications of Co-Crystals in Pharmaceutical Drugs.* Systematic Reviews in Pharmacy, 2018. **9**(1).
[33]. Airaksinen, S., et al., *Excipient selection can significantly affect solid-state phase transformation in formulation during wet granulation.* Aaps Pharmscitech, 2005. **6**: p. E311-E322.
[34]. Kumar Bandaru, R., et al., *Recent advances in pharmaceutical cocrystals: From bench to market.* Frontiers in Pharmacology, 2021. **12**: p. 780582.