Unlocking Potential: Cocrystals as catalyst for heightened solubility and dissolution of low solubility pharmaceuticals

Rohit Patil[1], Sachinkumar Patil[2], Sachin Mali[3]
[1,2,3] *Ashokrao Mane College of Pharmacy, Peth Vadgaon;416112, (M.S.) India*

***Abstract*—The abstract provides an overview of solubility in pharmaceuticals, emphasizing its significance and challenges. It discusses the importance of drug solubility in dosage frequency and bioavailability, highlighting the prevalence of solubility issues in marketed drugs. The framework for classifying biopharmaceuticals (BCS) categorizes medicines determined by solubility and permeability, guiding formulation strategies. Cocrystals offer a promising approach to address solubility challenges, providing a rational means to modify drug properties. The abstract explores the definition and potential of cocrystals in various applications, with a focus on pharmaceuticals. It examines the mechanisms of cocrystal formation and their impact on drug solubility enhancement. Various cocrystallization techniques, including solution-based and solid-state methods, are discussed, along with analytical techniques for characterization. Case studies on AZL-NA and lopinavir-menthol cocrystals highlight the efficacy of cocrystal technology in improving drug properties. Future prospects for cocrystal engineering involve overcoming commercialization challenges and scaling up production. Computer-assisted techniques and continuous processes offer promising avenues for advancing cocrystal technology. Overall, cocrystal engineering presents a viable strategy for enhancing drug solubility and bioavailability, potentially leading to the development of novel and improved pharmaceutical formulations.**

***Index Terms*—Bioavailability, Cocrystals, Drug formulation, pharmaceutical technology, Solubility.**

I. INTRODUCTION

Solubility is the proportion of a given solute in a given solvent that represents the analytic composition of a saturated composition." according to international organisation for applied and pure chemistry. [1] Additionally expressed as follows: " One substance's dexterity can completely dissolve into a different one with certain controlled situations like pressure and temperature." Grams/Liter are used to express it. An agent that dissolves is typically A little common portion of the remedy, whereas The dissolved substance is the small element of a liquid solution that has been dissolved. [2-5]

Importance of drug solubility

In order to address this, there will be a rise in dosing frequency. However, raising the regularity of medication administration will possess certain negative effects within the human frame because all medications have side effects, and the patient may begin to experience additional illnesses. If the drug has poor solubility, the amount needed the system's ability to act in the intended region will be fewer because you are administering a small amount, but the body will absorb much less than the given amount. Approximately 92% of medication on the marketplace posses solubility problems, and just 8% of medications can be solubility from class 1 to class 2. [6]

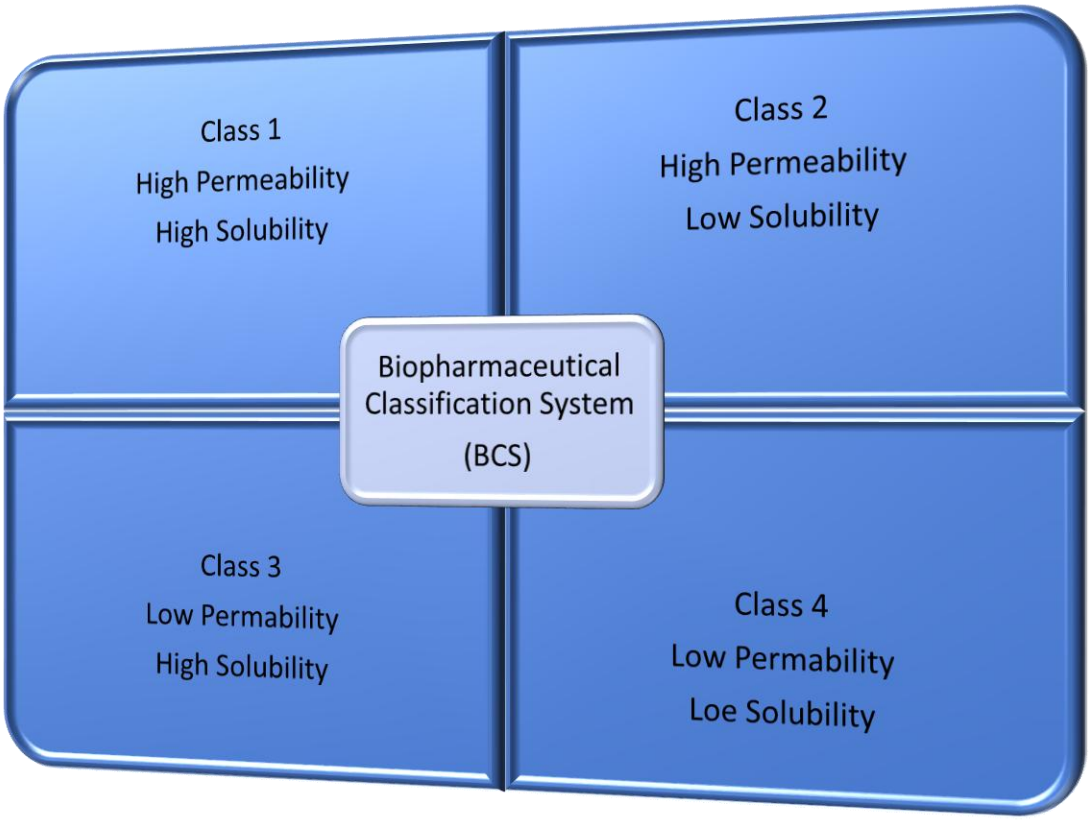

Figure 1: BCS Classification

Class Boundaries:
In order to analyse the border in this case, permeability and solubility are taken into account. The boundaries of each BCS class can change depending on the references. [3]

Solubility: The right medication should dissolve in aqueous fluids at 37 degrees Celsius with a solubility of 1 gramme per litre (g/L).

Permeability: The right medication should be able to pass through human bowel epithelial cells or one layer of Caco-2 cells with the permeability coefficient stands at times 10^{-6} centimeters per second.

Class first and Class third drugs are thought to have strong bioavailability, while Class second and Class fourth drugs occasionally need specific formulation to increase their absorption due to their poor bioavailability. [4] Cocrystallization, Solid variability, pro-drugs, micronization, complexation, and lipid-base compositions are used to modify drugs in Classes second and fourth. [6]

Table 1: Solubility Expression

Terms	Parts of solvent required for 1 part of solute
Very soluble	Less than 1 parts
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble	More than 10,000 parts

What is a co-crystal? [7]
The potential of cocrystallization in the carefully planned creation and processing of porous materials for uses involving gas preservation and segregation [8] or the logical manufacturing of ferroelectrics at equilibrium temperature. [9] It has ignited considerable enthusiasm, prompting deeper examination in large range of domain. Current works published have highlighted some of these intriguing

prospects. Attempts to create cocrystalline components for optical non-stationary operations have sparked curiosity in co-crystals of tiny molecules as a substance with as materials with altered characteristics. [10] and in the early 1990s, a set of guidelines controlling common chemicals' tendency to form co-crystals were clarified. [11,12]However, the most noticeable and possibly most sensible prospective influence of co-crystals is situated towards logical sense regulation of dosage and solid-state properties of pharmaceuticals [13–17] an extensive book on the topic has been written Regarding the definition of a co-crystal's possibilities utility in pharmaceutical solid-form dosing, co-crystals have also created a good deal of excitement and debate in recent years. [18] Definitions and nomenclature have dominated much of the discussion. Recently, Barbour et al. offered a clear and succinct overview of the problems. [19] and their definitions and recommendations are mostly used here. A multicomponent molecular crystal, or crystalline material made up of more than two chemically unique molecules, is referred to as a co-crystal. [20, 21] Solvents, This concept includes hydrates as well as featuring stoichiometric and non-equimolar lattice inclusions.

There exist attempts in the literature to concentrate on co-crystal research or, at the very least, to limit its scope. A feasible stipulation that has been suggested that all molecular components must be solids at ambient thermal level conditions. [22,23] Strictly speaking, this restriction would lead to multiple definitions of the same drug in labs with varying temperatures. Co-crystals containing solid co-formers differ from those that contain compounds that may have been unintentionally added since they could operate as a solvent for the pharmaceutical agent that is active (API) in a practical and "inventive" way. It has therefore been suggested that none of the components of a co-crystal should have served as a solvent during the crystallisation process. [19] Consequently, several researchers believe because solvent molecules present in multicomponent molecular crystals do not constitute "appropriate" co-crystals. Even if the intentional Co-crystal form is uncommon. concentrates regarding solvates in practice, this The difference is arbitrary and shouldn't be included in a formal explanation. It is accurate to say that well-known phrases that are already in use, like "hydrate" (used to describe multicomponent crystals that include water along with an additional substance) also "solvate" (used to describe multiple components crystals that include a chemical and a solvent that has crystallised from that solvent), represent subcategories of co-crystal. On the other hand, there is no conceptual difference between cocrystals of medicinal substances using solid co-crystal precursors, water, or solvents.

On the other hand, even though such enantiomers can be separated (at least in theory), crystals made up of different enantiomers of the identical substance material aren't typically recognised as cocrystals. This is due to the fact that symmetry in the space class (reversal, incorrect revolution, or gliding activities) allows for the relationship between the two enantiomers within the crystal. Additionally, it is widely acknowledged that because ions cannot be separated, salts containing twins of anion-cations do not form cocrystals. Even so, there is a "government health warning" attached to this requirement since temperature-dependent proton transfer has the potential to convert salts into cocrystals at varying warmth levels.

Pharmaceuticals Cocrystals

An API is essentially a cocrystal that contains another type of molecule called a cocrystal former as one of its molecular components, making it a medicinal cocrystal. More specifically, the part that isn't API needs to be non-hazardous and free of negative adverse consequences in order to be beneficial. In a perfect world, the cocrystal precursor would be mentioned included in the USFDA's "Anything Additional to meals in the US" records, which includes over 3000 materials generally accepted as safe/suitable for food additives. [24]

The reason pharmaceutical co-crystals are interesting is that they significantly increase the spectrum of solid forms that can be used in formulations, as they have crystal shapes that differ from the pure API. The bulk density index, nature, miscibility, and compressibility are among the physical attributes of cocrystals that vary. The liquefying temperature, the coefficient of friction, and the rate of disintegration. An amorphous or difficult-to-crystallize API can frequently be transformed into a manageable, stable crystalline solid by the formation of a co-crystal. Indeed, statistics indicate that less than one percent of candidates

medications ultimately arrive at the market. [25] Poor biopharmaceutical properties are considerably more likely to be the reason behind The potential active ingredient's failure in clinical studies as opposed to hazard or ineffectiveness. Although crystalline supplies are typically favoured due to their more convenient and repeatable characterization, lesser hygroscopic index, and good chemical index for stability, amorphous forms API are still employed as well as the foundation of a growing assortment of dosage types (examples like cefuroxime and rosuvastatin calcium). Significant potential exists for solubilizing a poorly soluble API through co-crystal formation. [10] But when dealing with highly soluble cocrystals, the solubility index should be taken with caution since the material can recrystallize into the most stable pure APIs when it comes into contact with a solvent.

Nevertheless, cocrystal formation doesn't necessarily increase the API solubilizing index since the less miscible forms inside the solvent they contain are referred to as solvate forms. [26] Reducing the solubility of very soluble active ingredient is crucial in the agricultural, chemicals field, since decreased solubility is necessary to stop the substance used in drainage systems from leaking too quickly. [25] This decreased solubility can also be a valuable characteristic.

Mechanism of cocrystal formation:

Rearranging molecules inside the crystal packing and creating and breaking noncovalent bonds are two aspects of crystal engineering. Consequently, it works well for creating supramolecular synthons. [27, 28] It eventually leads to the production of cocrystals, which could improve the physicochemical characters of API without changing its composition or operational mechanisms. Adipose groups, alcohol groups, and carboxylic acid groups are common functional groups involved in the production of supramolecular synthons by hydrogen bonding. [29, 30] Hetero-synthons are more likely than homo-synthons to produce co-crystals. [31, 32] Co-crystal formulations should involve non-ionic intermolecular interactions [29] that do not involve proton transfer.

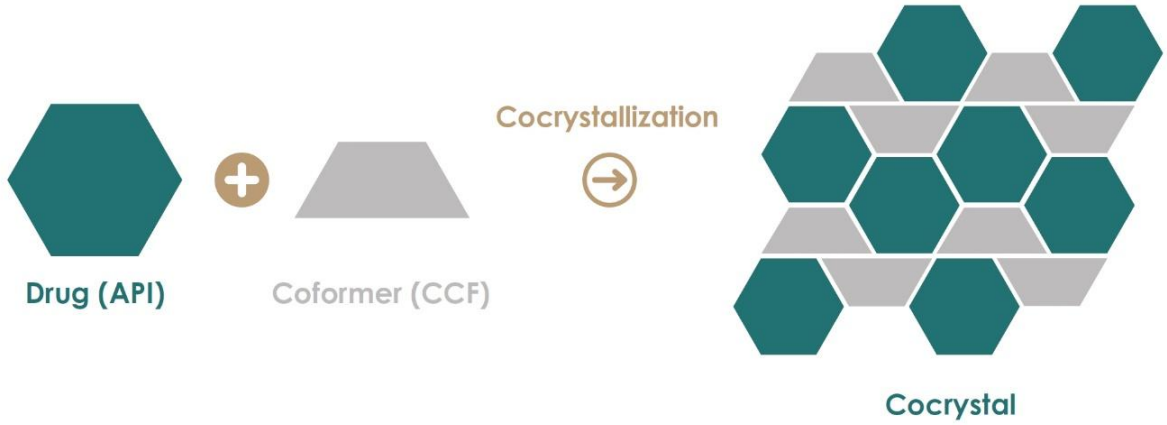

Figure 2: Pharmaceutical Cocrystal

Salt is formed if the proton transfer is successful. [33] The coformers pKa readings and API are the primary determinants of this proton transfer. pKa Δ are regarded as a cutoff point for differentiating from salt and cocrystals, according USFDA. [34] A threshold of Δ pKa is thought to be useful in differentiating between salt and co-crystals. Additionally, according to the FDA, components with Δ pKa values less than or equal to one will create salt. If the component with a Δ pKa less than one causes co-crystal formation. Apart from the FDA's recommendations, some sources stated that a "rule of thumb" indicates that if Δ pKa is lesser 2.7 to 3 unit, salt creation is more probable than cocrystal formation. [35] The pharmaceutical sector would benefit from adopting crystal engineering to fine-tune the properties of APIs. It was discovered that co-crystals outperform solvates, polymorphism, salts, and amorphous forms.

Mechanism involved in solubility enhancement:

Solubility is mostly determined by how robust the crystal lattice is additionally its solvent capacity. The lattice connections is weakened by cocrystals, while the solvent strength is increased. [36,37] Solvation primarily affects on cocrystals aqueous miscibility, which increases the drug's hydrophobicity. [38, 39] Most of cocrystals of hydrorepellent medicines have demonstrated worse miscibility than that ascertained using lattice energy as a result of this hydrophobicity.[40,37] Numerous investigations have related cocrystal miscibility with coformer solubility. This implies that the kind of coformers will determine the challenge to cocrystallization. [37,41]

Cocrystallization techniques:

Cocrystals have been produced by a range of techniques, like hot melt extrusion, solvent evaporation, reaction crystallisation, solid state grinding, and slurry conversion. Some of these methods have been documented. Yet, choosing an appropriate cocrystallization technique is still determined by making mistakes. To classify the most often used cocrystal formation techniques, both solution-contained and solid-contained procedures are typically employed. (Fig.3). When combining cocrystal ingradients in solution-based processes, a higher solvent demand is required. Additionally, the choice of solvent may change how the molecules of the Active Ingredients and the coformer interact, which affects the cocrystallization process. [42]

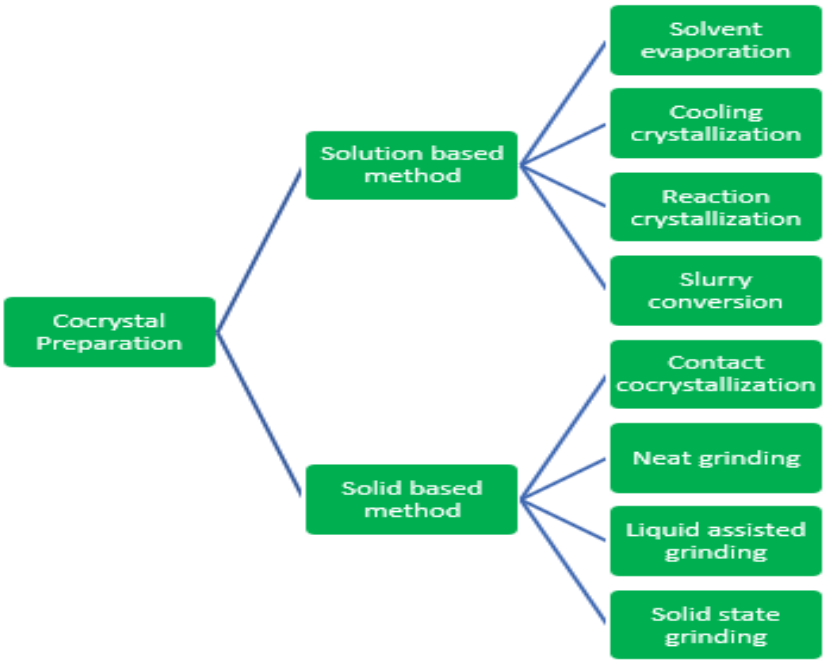

Figure 3: Methods For Cocrystallization Techniques.

Solution-based methods:

The solution in these procedures consists of three phases: solvent, coformer, and API. While supersaturation of the coformer, reactive materials, and API throughout the cocrystal process is ideal, the actual experimental conditions may result in either under- or oversaturation of these components. The crucial variable for the production of cocrystals in the mixed solution is the supersaturation level, which may be altered by varying the quantities of conformer and API. [42]

Solvent evaporization method:

The several popular technique for creating cocrystals is solvent vaporization, which is primarily utilised to create superior single crystals suitable for individual-crystal XRD architectural research. In order to create the cocrystal, this process entails completely breaking down the cocrystal constituents in an sufficient solvent at the proper stoichiometric ratios concentration and then vaporizing the solvent. [43]

Cooling crystallization:
The process of cooling crystallisation is one that is often employed to create large, pure crystals. In this approach, the local supersaturation explores the crystal features of distribution size, purity, morphology, and polymorphism. It is determined by procedure factors such as mass and heat energy transformation. [44] As a result, these factors need to be well controlled in conformative with many solid-liquid balance throughout the cocrystal procedure for development. The operational region during the crystallisation processes is established by the cocrystal's stoichiometry and the thermal-dynamic stability zone at the beginning and end thermal level. [45]

Reaction cocrystallization:
Reaction cocrystallization is a technique that may be used to create cocystals when the solubilities of the constituent parts vary. Cocrystal precipitation results from the combination of reactive agents with nonstoichiometric concentrations, which creates cocrystal supersaturated solution mixtures. In such a process, the initiation and creation of cocrystals are regulated by the reactants ability to diminish the solubility of the cocrystals. [46]

Slurry conversion:
The slurry conversion method involves adding extra cocrystal components to the solvent during the solution-mediated phase transition process. Each ingredient eventually dissolves into the slurry to generate A compound that facilitates the nucleation and development of cocrystals. Undersaturation and the capacity to further solubilize the cocrystal ingredients are caused by a decrease in reactant concentrations that occurs when cocrystals form. The third phase factor establishes the temperature operating range, concentration, and direction of cocrystal supersaturation formation. [47]

Solid-based methods:
In solid-state crystallisation, cocrystals are established spontaneously by interaction directly or mixing with greater dynamism inputs. This makes these procedures environmentally benign and efficient for producing cocrystals, since they use very little solvent. It becomes sense to look for options to solution-based cocrystallization techniques, which might be environmentally dangerous due to their high solvent usage. There are several solid-based methods for creating therapeutic cocrystals. [48]
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Contact cocrystals preparation:
After the raw materials were softly touched, It was shown that engagements within the coformer and API might happen in a natural way. A revised version that is a little bit more coherent and clear is provided here. The creation of eutectic phases, vapour diffusion between two solids, The sorption of hydrargy, amorphization, and long-range anisotropic molecular movement are some of the possible mechanisms that might lead to impulsive crystallisation upon contact. The creation of crystals is often aided by variables including higher humidity, higher temperatures, and the usage of smaller raw materials. [49,50,51]

Neat grinding:
Previous research has suggested that cocrystal formation during neat grinding may occur through the creation of a eutectic mix and/or a momentarily amorphous state in addition to molecular diffusion. [53, 54] The act of grinding creates a mobile solid surface through either vaporization or the transfer of energy, a phenomenon referred to as grinding-induced molecular diffusion. A requisite condition for an effective grinding process is the presence of a high vapor pressure from at least one component in the solid state. [52]

Liquid-assisted grinding:
Liquid-assisted grinding, as opposed to plain grinding, produces cocrystal products with higher production rates and better crystalline characteristics. Moreover, this method Regardless of the solubility of the constituents, this approach works well for quick cocrystal screening. To heighten molecular dispersion and hasten the building of cocrystals, a little amount of liquid may be included into the blend. The selection and quantity of liquid are crucial factors that impact crystal quality and additional solid byproducts produced during the mechanical-chemical process. [52]

Solid-state grinding:
In order to produce cocrystals, the solid-state grinding technique—which encompasses both simple and liquid-assisted grinding—is frequently utilised. The technique of creating a cocrystal without the need for

a solvent is known as "neat grinding," and it can be done manually (with a mortar and pestle), vibratory milling, or ball milling. The cocrystal is formed using liquid-assisted grinding, which involves grinding with a small quantity of solvent to aid. [52]

Analytical Technique:

Figure 4 displays the various instrumental analytical methods that were utilized to characterize the cocrystals.

Figure 4: Methods for Cocrystals Characterization.

X-ray diffractrometry (XRD) studies:

Unit cells linked to the cocrystal are examined using this instrument to identify their phase. For cocrystals, all of the architectural features may be obtained using powder and single-beam X-ray crystallography. However, powder XRD is commonly employed to determine various cocrystals by noting differences in the crystal lattice, whereas single crystal XRD is mostly utilised for architectural identification. The reason for this is because unique peaks are connected to unique co-crystals. Creating an individual crystal is the primary issue with single crystal XRD technology. [53] The substance is processed to produce a uniform finest powder for powder XRD. For assessing, adherence to Bragg's principle ($n\lambda=2d \sin \theta$) should be observed. [54]

Differential scanning calorimeter:

DSC is extensively employed to characterise co-crystals in the pharmaceutical sector. In order to ascertain if co-crystal formation is feasible, this approach involves heating the elements both in their pure form and as a cocrystal at a controlled frequency and closely examining the ensuing thermal graph. This approach produces a eutectic melt regardless of the drug-to-coformer ratio by using modest heating rates to crystallise the co-crystal before melting. [55] The thermal graph generated by the DS-Calorimetry scan is used for co-crystal screening because it allows co-crystal detection. The contrasts between the drug's pure thermogram and the coformer's show an exothermic signal in the former, and an exothermic pattern in the latter, followed by an endothermic peak, in the co-crystals' thermal graph. When cocrystals are compared to their pure component equivalents, they will show different melting points and fusion temperatures. A physical combination that is unable to produce cocrystals will only have one endothermic peak associated with eutectic melting on its thermogram. [56]

Spectroscopy:

When comparing co-crystals to pure elements, the co-crystals' chemical bonds will differ, allowing for different energy absorption or dispersion, which may be detected using NMR in vibrational spectroscopy

(IR and Raman). Comparing cocrystals to both the coformer and pure medicine, they have a distinct IR spectra with fewer peaks due to the hydrogen bonding that takes place between them. Hydrogen bonding has caused distinct differences between the bands of functional groupings. Solid nature NMR is frequently used to characterise the features of medicinal cocrystals due to its ability to offer architectural information about them. This technique is also applied to differentiate between salts and cocrystals since it permits measurement of the proton share. [57]

Field emission scanning electron microscopic study (FESEM):
SEM with field emission or topography is used to examine the surface anatomy of cocrystals. The contrast is achieved by using microscopic graphs of the components and cocrystals from the field emission SEM examinations. In lieu of thermal energy, the FESEM employs a "cold" supply. e^- are released from the conductor's surface more easily under an intence electric field. This method is made possible by the use of a tungsten filament as a cathode, which has a tiny, sharp needle with a diameter of between 10 and 100 nanometers. In order to get co-crystal micrographs, the field emission source and scanning electron microscope are combined. [58,59]

Hot Stage Microscopic characterization:
The two heat analyses and microscopic parameters are included in the HTM examination. Temperature and time fluctuations are examined with regard to the physicochemical properties of a solid state. Under a microscope, the cocrystal sample element, which was placed onto a glass substrate, changed during the heating process. These included changes in the melting and melting range as well as crystalline transition. [60]

II. CASE STUDY

Xingyi Zhu et al. 2022 research said that formation of the AZL-NA cocrystal via ball milling signifies a breakthrough in pharmaceutical cocrystal technology. Analytical tests confirmed its stable 1:2 stoichiometry, with enhanced solubility and dissolution rates over pure azilsartan. Despite slightly increased hygroscopicity, it promises improved drug delivery. Notably, in vitro dissolution enhancements translated to a remarkable 3.48-fold increase in bioavailability compared to pure AZL, showcasing its potential for oral formulations. This success highlights cocrystal technology's role in addressing pharmaceutical challenges, offering a pathway for advanced drug design and formulation. [61]

Noha d fayed et al. 2022 research said that The cocrystal was formed through the ethanol-assisted blending of lopinavir and menthol with superior dissolution rates versus the natural pure lopinavir. Optimal 1:2 M ratio enhanced dissolution without menthol phase separation. This method not only hastened lopinavir dissolution but also augmented its intestinal permeability, potentially improving absorption. Utilizing menthol as a co-former modified lopinavir's crystalline structure, facilitating faster dissolution and absorption. The study underscores co-crystal technology's efficacy in enhancing lopinavir's pharmaceutical properties vital for antiretroviral therapy. Through ethanol-assisted kneading and menthol co-forming, researchers advanced lopinavir formulation, offering promise for enhanced patient outcomes in antiretroviral treatment. [62]

Future aspects:
In the past decade, cocrystal engineering has gained prominence for improving the undesirable characteristics of pharmaceutical compounds. Some pharmacological cocrystals have gained FDA approval or entered clinical trials, yet challenges persist in their commercialization. Selecting suitable coformers is crucial but often involves laborious trial and error. Recently, computer-assisted techniques, such as artificial neural networks using data on the CSD, have emerged to expedite cocrystal screening. Designing cocrystals with desired properties necessitates a thorough understanding of their structural and physicochemical attributes. Considerations include pharmacokinetics, efficacy, toxicity, and compatibility with excipients. Scaling up production of high-purity cocrystals remains a challenge. Continuous processes, like twin-screw extrusion with in-line process control, offer promise for large-scale production. Overcoming these hurdles will facilitate the translation of cocrystal technology from the laboratory to commercial pharmaceutical applications, potentially offering novel and improved therapeutic options. [63,64]

III. CONCLUSION

In conclusion, solubility is a pivotal factor in pharmaceutical formulation, impacting drug efficacy and patient outcomes. The System of Biopharmaceutics Classification (BCS) categorizes drugs based on solubility and permeability, guiding formulation strategies to overcome challenges associated with poor solubility. Cocrystal engineering emerges as a promising solution, offering a rational approach to enhance drug properties without altering composition. Through various cocrystallization techniques and analytical methods like X-ray diffraction and spectroscopy, cocrystals have shown remarkable potential in improving drug solubility, dissolution rates, and bioavailability. Case studies on AZL-NA and lopinavir-menthol cocrystals underscore the significant advancements in pharmaceutical formulations facilitated by cocrystal technology.

Looking forward, addressing challenges in cocrystal commercialization and scaling up production is essential for widespread adoption in pharmaceutical applications. Advances in computer-assisted techniques and continuous manufacturing processes offer promising avenues for overcoming these hurdles and accelerating the development of cocrystal-based drug formulations. In summary, cocrystal engineering represents a promising strategy for enhancing drug solubility and bioavailability, offering potential benefits for patients and the pharmaceutical industry. To fully realise the medicinal value of cocrystals in drug development and formulation, more research and innovation in this area are essential.

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