REVIEW ARTICLE

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230 – 8407

ADVANCE TECHNIQUES OF CO-CRYSTALLIZATION - A REVIEW

Rajeev Kumar[1*], M.A. Sheela[1], Monika Sachdeva[1]

[1]Raj Kumar Goel Institute of Technology (Pharmacy), 5th KM Stone, Delhi-Meerut Road, Ghaziabad, U.P. 201003 India

*Corresponding Author E-mail: Rajeevsingh354@gmail.com

Article Received on: 17/06/2022 Approved for publication: 01/08/2022

DOI: 10.32937/2230-8407.3728

ABSTRACT

The two fundamental obstacles in developing novel products are poor water solubility and limited oral bioavailability. BCS classes II (Low solubility/High permeability) and IV (Low solubility/Low permeability) account for 60-70 percent of newly invented drugs. However, solubility and percentage of drug release are critical in determining drug molecules effectiveness. Several strategies are established to improve the solubility of poorly soluble pharmaceuticals, but their effectiveness relies on the drug's physical and chemical qualities. Cocrystallization techniques are one of the greatest approaches to addressing and enhancing the solubility of poorly soluble drugs. These are the multicomponent systems in which at least one component is a drug and others are carrier & pharmaceutical acceptable ingredients. It also significantly improves physicochemical attributes like solubility, permeability, stability, and bioavailability while preserving the pharmacological quality of active pharmaceuticals. This review presents an overview of pharmaceutical cocrystal classification, highlighting several advantages and applications of Pharmaceutical cocrystal, numerous cocrystal manufacturing procedures, and regulatory aspects. Additionally, analytical methods are discussed in this review for identifying cocrystals. This review will suggest a more productive design and production of pharmaceutical cocrystals with ideal physical and chemical properties and applications.

KEYWORDS: *Cocrystals, Bioavailability, Permeability, Cocrystallization, Regulatory Aspects, Patents*

INTRODUCTION

To define the effectiveness of a drug, solvability and % of drug release are the important aspects that play a vital role in the evolution and preparation of effective drugs in the pharmaceutical industry.[1] However, about sixty percent of medicines are synthesized, and the remaining forty percent of drugs possess solubility challenges that trigger bioavailability disputes and compatibility issues. Various strategies were proposed to boost the solubility and % of drug release of sparingly soluble drugs. the addition of cyclodextrins, solid dispersion, salt formation, micro emulsification, and the inclusion of complex formations contribute to improving the solubility profile of the drugs.[1,2]

Co-crystallization is one of the promising techniques used in the pharma sector that suffices in life cycle management through potential advantages of enhanced solubility, dissolution, bioavailability, permeability, and stabilization of unstable compounds via intermolecular interactions[3]. the Biopharmaceutical Classification System divides poorly soluble medications into classes BCS II & IV.[4]

Since pharmaceutical crystallization is also applicable to non-ionisable APIs, this adds an advantage in the era of salt formation technique.[2] Physically, the solid form of the drug can be obtained from an active pharmaceutical ingredient prepared by cocrystals that helps achieve an elevated dissolution amount in contrast to amorphous form crystals.[5]

Pharmaceutical cocrystals contain a couple of molecules or supplementary molecules, which H-bonding and stoichiometric ratio vow. Pharmaceutical cocrystals incorporate pharmaceutically acceptable conformational isomer and the drug substance into the same crystal network, which led to the origination of new composition of the API /APIs. In addition, it was identified that cocrystals are scrutinized as drug discrete instead of new APIs bearing a consequential impact on the drug.[6 7]

Advantages of Cocrystals[8]

- Physically, cocrystals are extremely firm compared to other anhydrous crystals and amorphous solids. Even

at high humid environments, they don't get converted to crystalline hydrate.

- API molecules in ionizable or non-ionizable forms can also be used as cocrystals.
- Conformers can be used as an ingredient in cocrystals. they also get along with different APIs followed by food additives and preservatives.
- Cocrystals are environment friendly as they are produced using solid-state synthesis and green technologies and never use derivate/solvents.

Cocrystal Applications

Improved Bioavailability of an API

Low drug bioavailability leads to ineffectiveness, whereas a higher drug dose can be toxic. the bioavailability of a drug is directly proportional to API's solubility and dissolution rates. Drugs with polymorphous forms are ten times more soluble than amorphous drug forms and in addition, crystal forms are a hundred times more soluble than amorphous ones.[9,10]

Increased Resistance to Hydrate Formation

Moisture availability in an API can lead to undesirable changes in physicochemical properties, such as low bioavailability. the API's production, formulation, packing, and storage conditions probability of moisture gaining persist as some challenging steps. Wet granulation, spray drying etc., can lead to hydration of the drug if hydrated excipients are used in the process of drug manufacturing.[11]

Improved Compaction Properties for Tabletting

Among all availability of API's, it is identified that only less than twenty percent of the Active Pharmaceutical Ingredients (API) can be converted into tablets through direct compression. However, most of the API's fluidity, cohesion, compatibility, compressibility, and lubricity are all qualities necessary for direct compression. [12] Through the process of cocrystallization, attempts were made to originate reliable API's that are pharmaceutically acceptable, thermodynamically stable and possess better compaction properties. API's like paracetamol cannot be converted into salt due to the absence of acidic and basic groups in the molecule. In view of the same, molecule such as paracetamol- trimethylglycine cocrystal, which is a biologically safe molecule, was produced by the mechanism of cocrystallization. [13]

CLASSIFICATION OF COCRYSTAL

the classification of cocrystals is largely based on the utility of individual medications. Scientists and researchers tend to focus on the structure's content rather than its utility. This is owing to the vast range of cocrystals applications, including several disciplines such as medical, paramedical, pharmaceuticals, agro chemistry, engineering, minerals, crystallography, and energy sectors. [14] [15]

Cocrystals are divided into two main classes:

a) Binary Cocrystals. (Form-1)

b) Polymorphic Cocrystals. (Form-2)

Binary cocrystals knew as duet components and solo solid crystalline constituents. they depend wholly on hydrogen bonding tendency, supramolecular synthons, parameters and values of Hansen dissolving w.r.t acidity of molecules etc.[16] Polymorphic cocrystals are the second class of cocrystals: Polymorphism is studied in solid-state chemistry.[17,18] Inspecting the polymorphism and its nature is an important part of the drug profile as polymorphic forms show diverse physical and organic properties. the same defines the forthcoming of manufactured drug formulation.[19,20,21] Solid illustrations of cocrystal polymorphism were initially witnessed when a chloroform solution of caffeine and glutaric acid was permitted to vaporize in a slow and steadily conditioned, two polymorphs having dissimilar morphologies rods (form I) and blocks (Form II) were produced.[22]

Salt cocrystals: Before the origination of cocrystals, salt creation was one method used to amend API's physical characteristics. Statistics demonstrate this. Approximately half of all drugs on the market are regulated in salt formulations.[1]

Solvated/hydrated cocrystals comprise an alternative category of multi-component molecular crystal. Aqua molecules are also part of that arrangement of crystals. In a few cases, visitor molecules retain a crystal composed and ruined upon disintegration. [21] [23]

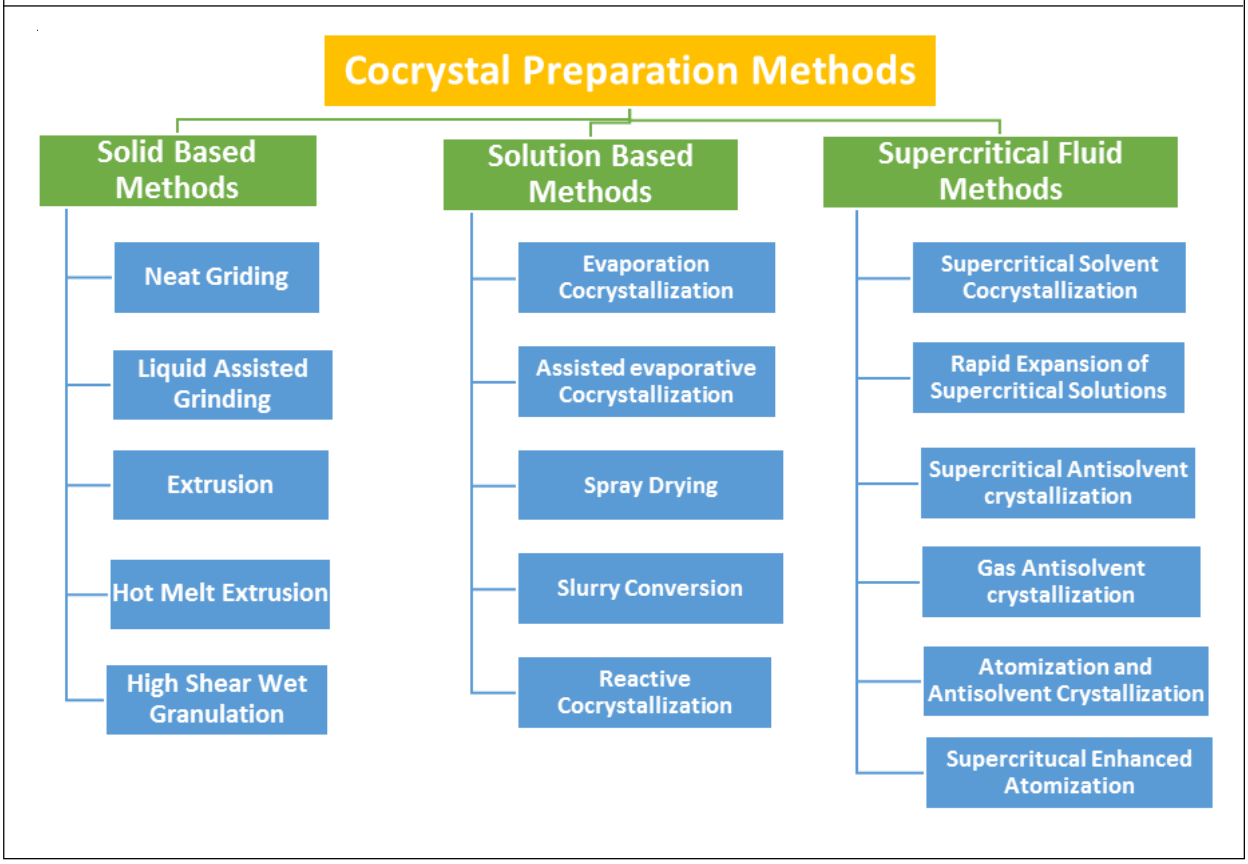
COCRYSTAL PREPARATION METHODS

the countless approaches used for the forming of cocrystals are generally categorized into binary groups named Solid-state methods and solution-based methods.[16]

Several popular techniques used to produce cocrystals, condensation, vaporization of solvent, anti-solvent addition, adjournment adaptation procedure and reaction crystallization approach have been depicted in Figure 1.

In recent times few fresh approaches have experimented with the development of cocrystals. That includes critical fluid atomization technique, area unit ultrasound aided

Figure 1: Preparation Methods for Cocrystals



methodology, spray-drying and the hot soften extrusion technique etc. had come into existence. [8]

Solid State Methods

Initially, cocrystals having solid-state formation have gained significant interest due to the rewards linked with these progressions, which mostly comprise solid-phase grinding, melt extrusion and sonication (applied to any dry or wet solid mixtures) starting at 80 to 85°C and complete process of cocrystal formation in the solid-state involves melting of API and co-former followed by mixing which leads to cocrystal foundation in a static stoichiometric ratio. Although, few are not suitable for thermo-labile components. However, it is a relaxed, ascendable uninterrupted route to preparing solid-state cocrystals.

Under a controlled environment, the collaboration process, active pharmaceutical ingredients and co-former resulted in the spontaneous development of the cocrystals. Moreover, it is also reported that in the case of pre-milled reactants, the rate of cocrystallization was faster than un-milled reactants. However, higher cocrystallization rates have been reported for the same system at higher temperatures and relative humidity, regardless of the mechanical activation. Cocrystallization mechanism in the occurrence of humidity in damp conditions usually entails three points: (1) wetness acceptance, (2) reactants split up (3) crystal seeding and evolution. [24]

Grinding in a solid-state

Grinding in Solid-state is categorized into two types, i.e. dry grinding and moistened grinding. the grinding method in the solid-state is a far better technique than others. [25] [26]

Neat (Dry) Grinding

In this type of grinding, cocrystal formation depends on mixing while applying pressure to a solid mixture of APIs and their co-formers. the mixing is by either with hand using a mortar-pestle or by machines like vibratory or ball milling can fulfil the job. Because of the best product quality, the temperature and mixing time are controlled, whereas the common grinding time ranges from 30 to 60 minutes. the advantage of this method is that it eliminates the need for solvent use so that no stability problem will occur. the main flaw is the low efficacy of cocrystal formation due to dry mixing. Some products will convert to an amorphous form, and the resultant sample will be impure and need further purification.[14,27]

Wet (Liquid-Aid) Wet Milling

A sufficient amount of liquid is incorporated into the solid powders before milling; solvents like water, ethanol, toluene etc., could be used in wet milling. Only a few microliters or drops of solvent are needed. This method is also called solvent drop grinding. It increases cocrystal formation as the liquid acts as a binding agent to bind solid powders rather than dissolve the media. This method is simple and effective in giving low-cost cocrystal with higher purity than other methods. Also, this method increases yield percentage in comparison to dry grinding.[14,27,28]

Solvent Drop Extrusion Technique

It is stated as the hot-melt extrusion technique, which is regularly engaged for the production of cocrystals in a single step as an unending manufacturing process. [29] thermodynamic stability of the compound usually defines the usage of subjected techniques which comprises the fusion of cocrystals devoid of the usage of solvent provides an extraordinary proficient involvement to develop surface contact.[8] In this method, the heat used for the excursion is established at a precise high temperature, wherein only the medium is slushy/ liquefied. Moreover, using the HME method, cocrystal establishment needs an inducing mediator to develop the cocrystal foundation. Appropriate matrices for the HME method require several qualities such as; (1) low glass transformation (Tag) temperature, inferior to liquefaction point of cocrystal to certify inferior processing condition, (2) restricted noncovalent interface with drug or co-former, (3) Shows speedy petrification step. the disadvantage of this method is that each co-former and active pharmaceutical are not suitable for certain unstable drugs.[30]

Solution Based Methods

these methods are more frequently used. they depend on adding a large amount of solvent in which both APIs and conformers should be dissolved. the crucial step in this method is the solvent selection process. Changing the solvent and temperature to give the best cocrystal characteristics would also be a challenge. [11] In solvent dependent crystallization method, the crystallization of the compound out of the solution may occur when the solvents become supersaturated with cocrystals. Thus the rate-limited step in the solvent-based method is when the degree of solvent unsaturation is lower than the cocrystallization rate.[12] Many methods are classified as solvent-based, such as solvent evaporation, slurring, active cocrystallization and anti-solvent, but the most important one is solvent evaporation.[11]

the Technique of Solvent Evaporation

the solvent evaporation technique is frequently used for cocrystal preparation as the same comprises of dissolving an equal number of mole amount of API and conformer in solvent mixtures. the solvent facilitates molecular interaction and bond formation; the evaporation will reveal the former cocrystal. the evaporation rate should be monitored carefully; rapid evaporation usually exerts a large number of small cocrystal, while a slow evaporation rate gives few large ones. Evaporation of the solvent occurs spontaneously at room temperature or by using accelerated techniques which depend on increased temperature and decreased pressure, such as rotatory evaporator and vacuum filtration. [14 31 32]

Slurry Crystallization

This methodology involves using the suspension, manufactured with the augmentation of various catalysts within the blend of active pharmaceutical ingredients and appropriate co-formers accompanying the same. In addition, the solvent is gradually poured and retained compact substance is dehydrated underneath a stream of N2 for five minutes and interpreted with Powder X-ray Diffraction. the slurry crystallization approach is cast-off for cocrystal formation only if the drug and co-former stand firm within the solvent. However, the subjected technique was also constrained as it involves the usage of solvent in larger amounts.[39 33] Prafulla et al. fused caffeine and maleic acid cocrystals by ultrasound-assisted slurry cocrystallization techniques.[34]

Rahman et al. explained the comparative study of acyclovir and succinic acid cocrystals by grinding and slurry technique. their findings suggest that the grinding approach, the produced cocrystals created by the slurry method, had a higher intensity of diffraction peak on X-ray diffraction than other grinding methods, and the maximum dissolving efficiency was reported at 15 minutes.[35]

Freezing Crystallization

the least technique used for producing cocrystals takes place slowly, utilizing large periods to process the linking. To further practices which contain examples as, Darunavir-succinic acid cocrystal. As per the stated example, solvability enhancement, % of drug release than its discrete drug Darunavir. A planned seeded refrigeration crystallization method was castoff to prepare cocrystals of carbamazepine: nicotinamide from ethanol wherein main parameters such as solvent selection, thermos-dynamical stability of Cocrystal functioning. Spans followed by supersaturation of actives are considered a key to the design of this process. [26]

Anti-Diluent Method

This method is used to fuse high excellence cocrystals, also known as the vapour diffusion method. the subjected method involves using a moderator in which the admixture is not as much as the dissolved one. It is often added to the alternative suspension, favouring the solid settling. Supersaturation is created by adding subsequent fluid to the drug-conformer fluid, which leads to condensation, and the same is mixable in the fluid to form cocrystals. these cocrystals are insolvable or intermittently emulsifiable. Moreover, this method also has one disadvantage due to its steady act, compared to crushing and the consumption of bulky capacity of dissolvent. [36] To identify the ideal absorption (e.g., the proportion of dissolvent to anti-diluent) for the foundation of cocrystals, phase solubility diagram construction is an integral part of the methodology. In several scenarios, a co-former dissolvent is adjoined to the drug, a biological solution to ease cocrystallization. the subjected method is predominantly used to settle the excipients and the crystal's main component. [37]

Crystallization by Reaction

This procedure involves the nucleation process followed by the cocrystallization process, which is usually governed by the cocrystal component and their dispersible act. the main aim of this learning is to inhibit the usage of any additional drug or co-former in the opening solutions, which can be recognised as a cocrystal. Correspondingly, due to the component's solvable constrains, the precipitated cocrystals are unadulterated.

Spray-Drying or Freeze-Drying

Mixtures prepared using freeze-drying API–conformer solutions can also produce cocrystals. these processes have faster solute solidification than aqueous solution crystallisation. they may be promoted by minimizing phase separation followed by precipitation of low solvability constituents due to the same cocrystal formation. This method is projected to make pharmaceutical cocrystal manufacturing on a massive scale possible through accelerated conditions, profitable dissolvent evaporation etc. This method is appropriate for manufacturing injectables containing solid particles aseptic. the restriction was also associated with this method as subjected method generated unstable solids in undefined lattice or metastable crystals.[38,39,40]

VARIOUS TYPES OF COCRYSTAL FORMATION

Treatment with a Laser Beam

This technique uses a dense carbon-di-oxide light beam for exposing powder blends to radiation for recrystallization configuration. Titapiwatanakun et al. had. Used the subject procedure for yielding caffeine cocrystals with malonic and oxalic acid. they stated that the cocrystal structures need to be identical to a significant amount for the cocrystallization step, which directs that in the vapour phase, the procedure of the particle reordering among the drug, its particle structure and the origination of the co-crystal.[41]

Ultrasound-assisted Cocrystallization

This novel method involves ultrasound waves; these waves facilitate phase transformation processes leading to cocrystal production in a short time as it induces nucleation in solution. [42 43] Ultrasound apparatus or Sonicater found in two forms ultrasonic probe and ultrasonic bath.

the ultrasonic probe consists of a solid probe and sono-reactor vessel with a temperature controller. Aher et al. tried to prepare different molar ratios of Caffeine: maleic acid cocrystal using the ultrasonic probe; the probe operates at constant vibration equal to 20 kHz. Caffeine and maleic acid feed into the vessel in the form of solution or slurry with methanol as a solvent; then, the ultrasonic probe plays in a cycle of alternative ultrasound pulses (10 sec) with relaxation time (2 sec). Circulation of cold water from a water bath through a glass jacket may need to avoid excess heating. the resultant product was filtrated to give the required cocrystal. A cocrystal of 1,3,7-Trimethylpurine-2,6-dione \ cis-butenedioic acid in a two to one (2:1) ratio is prepared by using this method. [44]

An ultrasonic bath is a vibration-generating water bath. the powders will be dissolved in the solvent in a glass vial which will be sonicated at a controlled temperature until a clear solution is obtained. After that, the sonicate will turn off, and the solution will be filtrated to reveal the cocrystal. [45] Rodrigues et al. formed hydrochlorothiazide cocrystals with different conformers using an ultrasonic bath. the physical mixture of API and co-former was distributed in a solvent and sonicated in the ultra-sonic bath for 4 hours at 40 °C. after that, the solvent was left to vaporize at ambient temperature, and the cocrystals were harvested for further characterization.[46]

Microwave-assisted Cocrystallization:

Microwave radiations cause excitation and increase

molecular mobility by interacting with these radiations. the molecule's revolving dipoles will lead to rapid cocrystallization as the radiation heat maintains a supersaturated solvent and ensures its evaporation in a short time.[47]

Microwaves generating sources that can be used in cocrystallization are either: a domestic microwave or a microwave reactor. (Monowave 300, Anton Paar GmbH, Austria). A microwave reactor differs from the domestic one as the power and pressure produced by the reactor can be controlled precisely.[48,49]

the APIs and conformer powders will be dissolved in a suitable solvent depending on dielectric properties and solubility profiles. then the sample will transfer to glass tubes and set in the microwave to the required temperature, time and power. At the end, the solution is filtered to give cocrystal.[47]

IDENTIFICATION OF COCRYSTALS

For the identification of cocrystals, several instrumental analytical techniques were regularly used for the identification of pharmaceutical cocrystals and the elucidation of interactions between molecules.

Single-crystal and Powder X-ray Diffraction (XRD)

This method is the oldest and one of the most precise, known as the rotating crystal method. This instrument comprises a turn table, an x-ray source of light, a slight for a narrow beam of x-ray and a single crystal. Moreover, major in adherence lies with subjected methodology in procuring a single crystal. [50] [31] [51] Whereas in the powder diffraction method, the diffraction pattern is obtained from the powder of the material rather than an individual crystal.

thermal Analysis

Subjected methodology signifies various techniques that identify the physical and chemical changes to the sample thermal characteristics over time and in a controlled environment via programmed temperature change. (e.g., heating, cooling, alternating, or maintaining at a constant temperature) For cocrystal characterization, frequent methodologies involve Differential Scanning Calorimetry (DSC) and Hot-Stage Microscopy (HSM). Moreover, a brief w.r.t operating of DSC and HSM for the characterization of cocrystals is elaborated below:

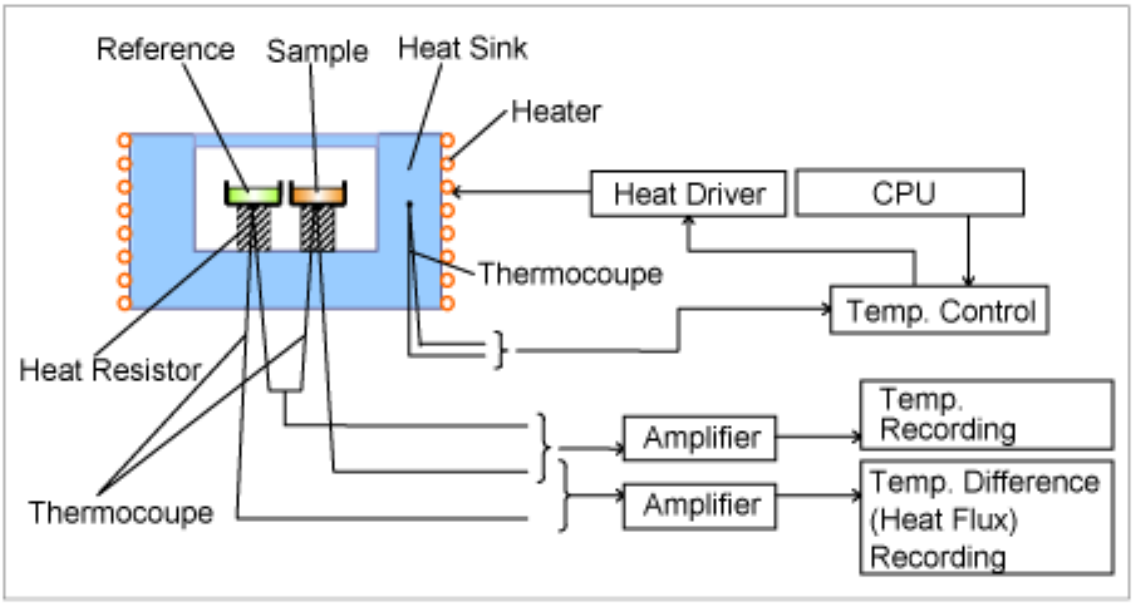
1. Differential Scanning Calorimetry (DSC)

This technique is used to study the behaviour of polymers/ samples on heating, and obtained thermogram is scrutinized to check the possibility of cocrystal formation.[3] . the pictorial representation of the methodology above is depicted below:

2. Hot Stage Microscopy

HSM is a powerful method to visually examine and capture

Figure 2: Schematic Diagram of DSC



all kinds of thermal transitions such as colour change, melting, polymorphism and polymer crystallization. Moreover, the subjected method is a simple and relatively inexpensive technique. [31]

Spectroscopy

the spectroscopic method is of two kinds types for the characterization of cocrystal, and the same is elaborated below:

a) Vibrational spectroscopy.

b) Nuclear magnetic resonance (NMR)

Vibrational spectroscopy measures the interaction of infrared radiation with matter through absorption, emission or reflection. This technique is based on periodic changes in dipole moments or polarizabilities.[52,53]

Nuclear magnetic resonance (NMR) exploits the magnetic properties of certain nuclei to study the compound's physical, chemical and biological properties.

Field Emission Scanning Electron Microscopy (FESEM)

This subjected methodology is frequently used in electron microscopes, whereas microscopic characteristics are determined by focus electron beam which passes through different electromagnetic lenses and apertures in high vacuum conditions.[54,55]

REGULATORY ASPECTS OF COCRYSTALS

the guideline for Pharmaceutical cocrystals and their formulations are regulated, and this has a significant impact on development and quality control procedures, as well as the value of intellectual property and procedure of cocrystal development, screening and applications are shown below: (Figure 9) [56] Because the solvates are of the initial drug substance, the provisions for pharmaceutical cocrystals are comparable to those for polymorphs of an API. It is not, in particular, considered a new API. With these guidelines, the pharmaceutical industries can produce cocrystals at established formulation facilities using APIs & co-formers without violating any current good manufacturing practice requirements (cGMPs). Moreover, drug manufacturers must submit appropriate data for new drug applications (NDAs) and abbreviated NDAs (ANDAs) possessing a co-crystalline form supporting the structure of the cocrystals. Data should show no ionic interaction between the API component and co-formers for APIs and co-formers with ionizable functional groups. Furthermore, before reaching the site of pharmacological activity, the API should be significantly dissociated from its cocrystal form.

In May 2015, the European Medicines Agency (EMA) published a reflection report that divided solid-state materials based on their internal structure and addressed the use of API cocrystals in medical products. EMA claims that cocrystals are "homogeneous (single-phase) crystalline structures comprising two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)."[57]

Figure 3: NMR Diagrammatic Representation

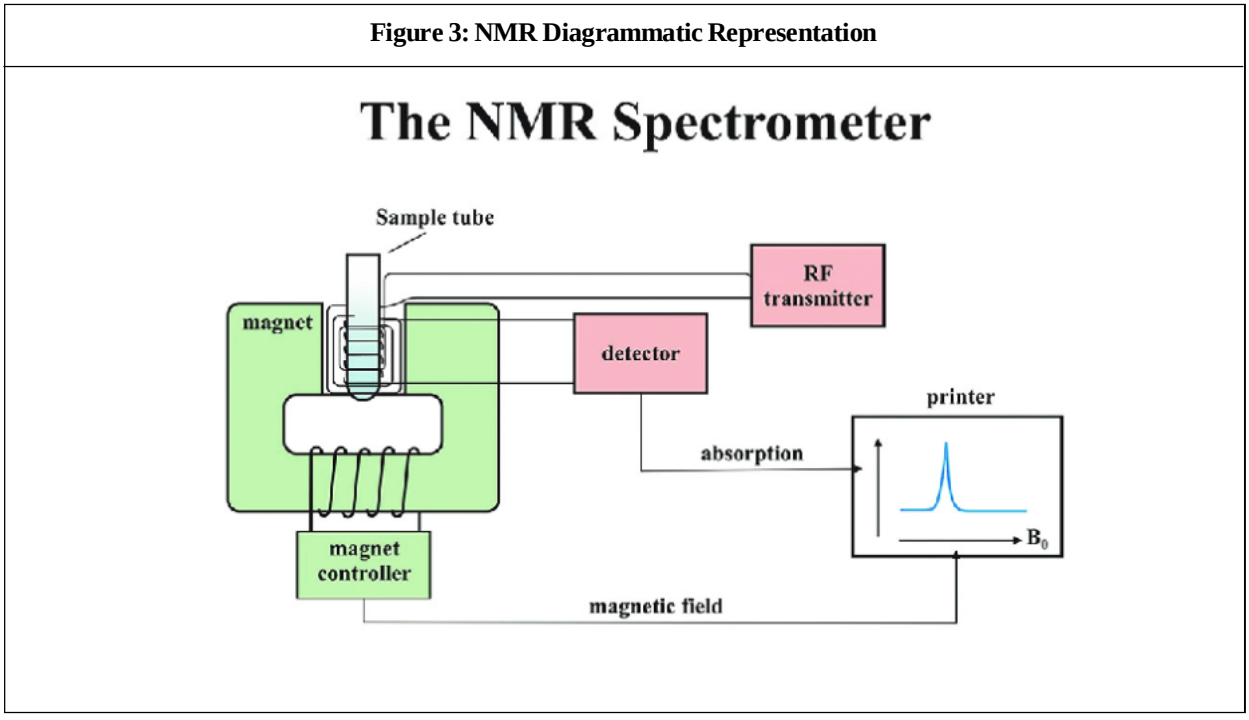


Figure 4: Diagrammatic Overview of Field Emission Electron Microscopy

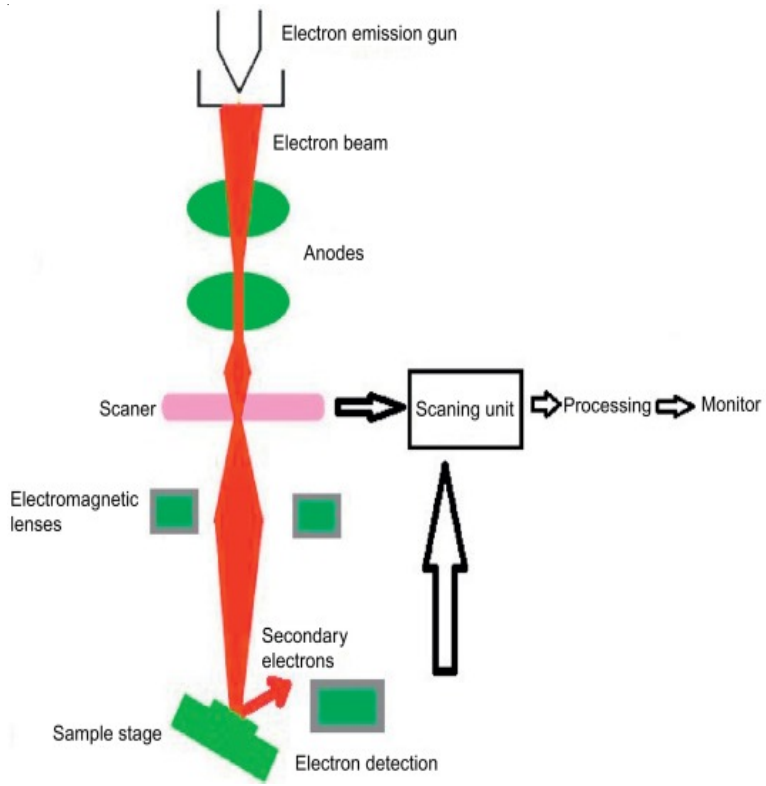
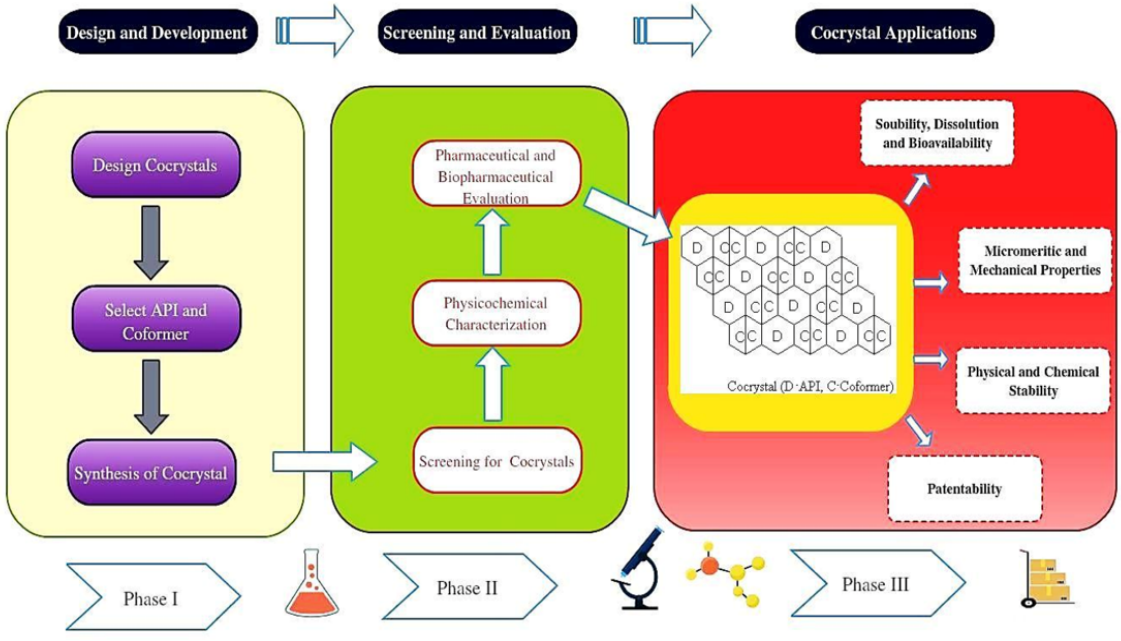


Figure 5: Cocrystal Development, Selection and Application



PATENTS ISSUED IN THE US AND EUROPE PHARMACEUTICAL CO-CRYSTALS

CONCLUSION

Cocrystallization techniques have become a vital tool for

Figure 10: Patents issued in USA and Europe

Patent No.	Title	Date	Assignee
US6001996	Complexes of cephalosporins and carbacephalosporins with parabens	December 14, 1999	Eli Lilly & Co., Inc. [58]
US7446107	Crystalline forms of conazoles and methods of making and using the same	November 4, 2008	TransForm Pharmaceuticals, Inc. [59]
US7625910	AZD1152; a phosphate prodrug and maleic acid cocrystal	Dember 1, 2009	Astra Zeneca AB [60]
EP1755388B1	Mixed cocrystals of modafinil	October 6, 2010	TransForm Pharmaceuticals, Inc. [61]
EP2185546B1	Cocrystals and pharmaceutical compositions, telaprevir (VX-950)	October 26, 2011	Vertex Pharmaceuticals, Inc. [62]
EP2334687B1	SGLT-2 inhibitors, l-proline and pyroglutamic acid cocrystals	January 4, 2012	Pfizer Inc. [63]
US8097592	SGLT-2 Inhibitor, l-proline cocrystal	January 17, 2012	Astellas Pharma Inc., Kotobuki Pharmaceutical Co. Ltd. [64]
EP2300472B1	Glucocorticoid analogues, phosphoric acid and acetic acid cocrystals	January 18, 2012	Boehringer Ingelheim Intl. GmBH [65]
EP2288606B1	Rivaroxaban cocrystal with malonic acid	February 15, 2012	Bayer Pharma Ag [66]
US8124603	Meloxicam with various carboxylic acids, aliphatic and aromatic, and maltol and ethyl maltol	February 28, 2012	Thar Pharmaceutical [67]
US8163790	Metronidazole cocrystals with gentisic acid and gallic acid (specific x-ray reflections in each case) and a cocrystal of imipramine HCl and (+)-camphoric acid	April 24, 2012	New Form Pharmaceuticals, Inc. [68]
US20170044176 A1	Cocrystal of tiotropium bromide and lactose monohydrate	February 16, 2017	Euticals Spa [69]
US20170224724 A1	Co-crystal (ICC) of lithium with salicylic acid and l-proline	August 10, 2017	University Of South Florida [70]
US20170101433 A1	Co-crystal of progesterone and a co-former selected from the group consisting of vanillic acid, benzoic acid, salicylic acid, cinnamic acid, and vanillin.	April 13, 2017	Amri Sci. Llc. [71]

an engineered crystal to regulate the properties of solid-state materials. Co-crystallization is a multi-beneficial approach with direct application to the pharmaceutical industry. In the future pharmaceutical cocrystals will be one of the important solid forms of pharmaceuticals that should be available in the market for faster bioavailability. Cocrystal formation provides high scope for controlled modified pharmaceutical properties such as dissolution rate, solubility, compressibility, stability, bioavailability and permeability. the difficulties include scaling up pharmaceutical cocrystal production, which will result from new scale-up techniques and high-throughput screening of potential cocrystals with various co-formers and polymorphs.

CONFLICT OF INTEREST

the authors have no conflict of interest.

REFERENCES

Schultheiss N. and Newman A. Pharmaceutical Cocrystals and their Physicochemical Properties. *Cryst Growth Des*. 2009; 9(6): 2950-2967. doi:10.1021/cg900129f

Kuang W., Ji S., Wang X., Zhang J. and Lan P. Relationship Between Crystal Structures and Physicochemical Properties of Lamotrigine Cocrystal. *Powder Technol*. 2021; 380: 18-25. doi:10.1016/j.powtec.2020.11.039

Bolla G. and Nangia A. Pharmaceutical Cocrystals: Walking the Talk. *Chem Commun*. 2016; 52(54): 8342-8360. doi:10.1039/c6cc02943d

Shan N., Perry M. L., Weyna D. R. and Zaworotko M. J. Impact of Pharmaceutical Cocrystals: the Effects On Drug Pharmacokinetics. *Expert Opin Drug Metab Toxicol*. 2014;10(9):1255-1271. doi:10.1517/17425255.2014.942281

Hickey M. B., Peterson M. L., Scoppettuolo L. A., *et al*. Performance Comparison of A Cocrystal of Carbamazepine With Marketed Product. *Eur J Pharm Biopharm*. 2007; 67(1): 112-119. doi:10.1016/j.ejpb.2006.12.016

Qiao N., Li M., Schlindwein W., Malek N., Davies A. and Trappitt G. Pharmaceutical cocrystals: An overview. *Int J Pharm*. 2011;419(1-2):1-11. doi:10.1016/j.ijpharm.2011.07.037

Tomaszewska I., Karki S., Shur J., Price R. and Fotaki N. Pharmaceutical Characterisation and Evaluation of Cocrystals: Importance of In Vitro Dissolution Conditions and Type of Coformer. *Int J Pharm*. 2013; 453(2): 380-388. doi:10.1016/j.ijpharm.2013.05.048

Sanjay A. N. Pharmaceutical Cocrystallization/: A Review. 2014;1(3):1074-1085.

Childs S. L., Kandi P. and Lingireddy S. R. Formulation of a Danazol Cocrystal with Controlled Supersaturation Plays an Essential Role in Improving Bioavailability. Published online 2013.

Shilpa C., Sarika N., Neetu K. and Shubham W. *Journal of Drug Delivery and therapeutics Cocrystals/: A Review Solubility*. 2018; 8: 350-358.

Rodrigues M., Baptista B., Lopes J. A. and Sarraguça M. C. Pharmaceutical cOcrystallization Techniques. Advances and Challenges. *Int J Pharm*. 2018; 547(1-2): 404-420. doi:10.1016/j.ijpharm.2018.06.024

Ulrich J. and Frohberg P. Problems, Potentials and Future of Industrial Crystallization. *Front Chem Sci Eng*. 2013; 7(1): 1-8. doi:10.1007/s11705-013-1304-y

Maeno Y., Fukami T., Kawahata M., *et al*. Novel Pharmaceutical Cocrystal Consisting of Paracetamol and Trimethylglycine, A New Promising Cocrystal Former. *Int J Pharm*. 2014; 473(1-2): 179-186. doi:10.1016/j.ijpharm.2014.07.008

Karimi-Jafari M., Padrela L., Walker G. M. and Croker D. M. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. *Cryst Growth Des*. 2018;18(10):6370-6387. doi:10.1021/acs.cgd.8b00933

Braga D., Grepioni F. and Maini L. the Growing World of Crystal Forms. *Chem Commun*. 2010; 46(34): 6232-6242. doi:10.1039/c0cc01195a

Kumar S. and Nanda A. Approaches to Design of Pharmaceutical Cocrystals: A Review. *Mol Cryst Liq Cryst*. 2018; 667(1): 54-77. doi:10.1080/15421406.2019.1577462

Sekhon B. S. Drug-drug Cocrystals. *DARU, J Pharm Sci*. 2012;20(1):1-2. doi:10.1186/2008-2231-20-45

Najar A. A. and Azim, Y. Pharmaceutical Cocrystals: A New Paradigm of Crystal Engineering. *J Indian Inst Sci*. 2014; 94(1): 45-67.

Babu N. J., Reddy L. S., Aitipamula S. and Nangia A. Polymorphs and polymorphic cocrystals of temozolomide. *Chem - An Asian J*. 2008; 3(7): 1122-1133. doi:10.1002/asia.200800070

Lemmerer A., Adsmond D. A., Esterhuysen C. and Bernstein J. Polymorphic Cocrystals From Polymorphic Cocrystal Formers: Competition Between Carboxylic Acid"Pyridine and Phenol"Pyridine Hydrogen Bonds. *Cryst Growth Des*. 2013; 13(9): 3935-3952. doi:10.1021/cg4006357

Lange L., Lehmkemper K. and Sadowski G. Predicting the

Aqueous Solubility of Pharmaceutical Cocrystals As A Function of Ph and Temperature. *Cryst Growth Des*. 2016;16(5):2726-2740. doi:10.1021/acs.cgd.6b00024

Trask A. V., Samuel Motherwell W. D., Jones W. Pharmaceutical Cocrystallization: Engineering A Remedy For Caffeine Hydration. *Cryst Growth Des*. 2005; 5(3): 1013-1021. doi:10.1021/cg0496540

Bhatt P. M., Azim Y., Thakur T. S. and Desiraju G. R. Cocrystals of the Anti-hiv Drugs Lamivudine and Zidovudine. *Cryst Growth Des*. 2009; 9(2): 951-957. doi:10.1021/cg8007359

Jayasankar A., Good D. J., Rodríguez-Hornedo, N. Mechanisms by which Moisture Generates Cocrystals. *Mol Pharm*. 2007; 4(3): 360-372. doi:10.1021/mp0700099

Karki S., Frišèiæ T., Jones W. and Motherwell W. D. S. Screening for Pharmaceutical Cocrystal Hydrates Via Neat and Liquid-assisted Grinding. *Mol Pharm*. 2007; 4(3): 347-354. doi:10.1021/mp0700054

Kaupp G. Mechanochemistry: the Varied Applications of Mechanical Bond-breaking. *CrystEngComm*. 2009; 11(3): 388-403. doi:10.1039/b810822f

Frišèiè T. and Jones W. Recent Advances In Understanding the Mechanism of Cocrystal Formation Via Grinding. *Cryst Growth Des*. 2009; 9(3): 1621-1637. doi:10.1021/cg800764n

Weyna D. R., Shattock T., Vishweshwar P., Zaworotko M. J. Synthesis and Structural Characterization of Cocrystals and Pharmaceutical Cocrystals: Mechanochemistry Vs Slow Evaporation From Solution. *Cryst Growth Des*. 2009; 9(2): 1106-1123. doi:10.1021/cg800936d

Kelly A. L., Halsey S. A., Bottom R. A., Korde S., Gough T, and Paradkar A. A Novel Transflectance Near Infrared Spectroscopy Technique For Monitoring Hot Melt Extrusion. *Int J Pharm*. 2015; 496(1): 117-123. doi:10.1016/j.ijpharm.2015.07.025

Li S., Yu T., Tian Y., Lagan C., Jones D. S. and Andrews G. P. Mechanochemical Synthesis of Pharmaceutical Cocrystal Suspensions via Hot Melt Extrusion: Enhancing Cocrystal Yield. *Mol Pharm*. 2018; 15(9): 3741-3754. doi:10.1021/acs.molpharmaceut.7b00979

Karagianni A., Malamatari M. and Kachrimanis K. Pharmaceutical Cocrystals: New Solid Phase Modification Approaches For the Formulation of APIs. *Pharmaceutics*. 2018;10(1):1-30. doi:10.3390/pharmaceutics10010018

Elbagerma M. A., Edwards H. G. M., Munshi T. and Scowen I. J. Identification of a New Cocrystal of Citric Acid and Paracetamol of Pharmaceutical Relevance. *Cryst Eng Comm*. 2011; 13(6): 1877-1884. doi:10.1039/c0ce00461h

Douroumis D., Ross S. A. and Nokhodchi A. Advanced Methodologies for Cocrystal Synthesis. *Adv Drug Deliv Rev*. 2017; 117: 178-195. doi:10.1016/j.addr.2017.07.008

Apshingekar P. P., Aher S., Kelly A. L., Brown E. C. and Paradkar A. Synthesis of Caffeine/Maleic Acid Co-crystal by Ultrasound-assisted Slurry Co-crystallization. *J Pharm Sci*. 2017; 106(1): 66-70. doi:10.1016/j.xphs.2016.09.009

Rahman F., Winantari A. N., Setyawan D., Siswandono. Comparison Study of Grinding and Slurry Method On Physicochemical Characteristic of Acyclovir – Succinic Acid Cocrystal. *Asian J Pharm Clin Res*. 2017; 10(3): 153-158. doi:10.22159/ajpcr.2017.v10i3.15925

Savjani J. Co-crystallization: An Approach To Improve the Performance Characteristics of Active Pharmaceutical Ingredients. *Asian J Pharm*. 2015; 9(3): 147-151. doi:10.4103/0973-8398.160309

Ober C. A. and Gupta R. B. Formation of itraconazole-Succinic Acid Cocrystals By Gas Antisolvent Cocrystallization. *AAPS PharmSciTech*. 2012; 13(4): 1396-1406. doi:10.1208/s12249-012-9866-4

Walsh D., Serrano D. R., Worku Z. A., Norris B. A. and Healy A. M. Production of Cocrystals In An Excipient Matrix By Spray Drying. *Int J Pharm*. 2018; 536(1): 467-477. doi:10.1016/j.ijpharm.2017.12.020

Alhalaweh A., Kaialy W., Buckton G., Gill H., Nokhodchi A. and Velaga S. P. Theophylline Cocrystals Prepared By Spray Drying: Physicochemical Properties and Aerosolization Performance. *AAPS PharmSciTech*. 2013; 14(1): 265-276. doi:10.1208/s12249-012-9883-3

Dixit M., Kulkarni K. P. and Selvam R. P. Review on: Freeze Drying As A Crystallization Technique. *Elixir Pharm*. 2011; 41(January 2011): 5717. https://www.researchgate.net/publication/283447469

Titapiwatanakun V., Basit A. W. and Gaisford S. A New Method for Producing Pharmaceutical Co-crystals: Laser Irradiation of Powder Blends. *Cryst Growth Des*. 2016; 16(6): 3307-3312. doi:10.1021/acs.cgd.6b00289

Deora N. S., Misra N. N., Deswal A., Mishra H. N., Cullen P. J. and Tiwari B. K. Ultrasound for Improved Crystallisation in Food Processing. *Food Eng Rev*. 2013; 5(1): 36-44. doi:10.1007/s12393-012-9061-0

Sathisaran I. and Dalvi S. V. Engineering Cocrystals of Poorlywater-soluble Drugs To Enhance Dissolution In Aqueous Medium. *Pharmaceutics*. 2018; 10(3). doi:10.3390/pharmaceutics10030108

Aher S., Dhumal R., Mahadik K., Paradkar A. and York P. Ultrasound Assisted Cocrystallization From Solution (Ussc) Containing A Non-congruently Soluble Cocrystal Component Pair: Caffeine/Maleic Acid. *Eur J Pharm Sci*. 2010; 41(5): 597-602. doi:10.1016/j.ejps.2010.08.012

Cruz R. M., Boleslavská T., Beránek J., *et al*. Identification and Pharmaceutical Characterization of A New Itraconazole Terephthalic Acid Cocrystal. *Pharmaceutics*. 2020; 12(8): 1-18. doi:10.3390/pharmaceutics12080741

Rodrigues M., Lopes J. and Guedes A., Sarraguça J, Sarraguça M. Considerations on High-throughput Cocrystals Screening By Ultrasound Assisted Cocrystallization and Vibrational Spectroscopy. *Spectrochim Acta - Part A Mol Biomol Spectrosc*. 2020; 229(xxxx): 117876. doi:10.1016/j.saa.2019.117876

Pagire S., Korde S. and Ambardekar R., *et al*. Microwave Assisted Synthesis of Caffeine/Maleic Acid Cocrystals: the Role of the Dielectric and Physicochemical Properties of the Solvent. *CrystEngComm*. 2013; 15(18): 3705-3710. doi:10.1039/c3ce40292d

Nugrahani I., Utami D., Ayuningtyas L., Garmana A. N. and Oktaviary R. New Preparation Method Using Microwave, Kinetics, In Vitro Dissolution-Diffusion, and Anti-Inflammatory Study of Diclofenac- Proline Co–Crystal. *ChemistrySelect*. 2019; 4(45): 13396-13403. doi:10.1002/slct.201903342

Yu X., Pu H. and Qing L. Y. Microwave Assisted Synthesis, and Structure of A Cocrystal Nickel Complex With 2-ethoxy-6-methyliminomethyl-phenol. *Mol Cryst Liq Cryst*. 2015; 607(1): 242-249. doi:10.1080/15421406.2014.930223

Lapidus S. H., Stephens P. W., Arora K. K., Shattock T. R., Zaworotko MJ. A Comparison of Cocrystal Structure Solutions From Powder and Single Crystal Techniques. *Cryst Growth Des*. 2010; 10(10): 4630-4637. doi:10.1021/cg1009237

Kumar S, Nanda A. Pharmaceutical Cocrystals: An Overview. Indian J Pharm Sci., 2017; 79(6): 858-71. doi: 10.4172/ pharmaceutical-sciences.1000302.

Vogt, F.G.; Clawson, J. S. Strohmeier, M. Edwards, A.J. Pham, T. N. Watson, S.A. Solid-State NMR Analysis of Organic Cocrystals and Complexes. Cryst. Growth Des. 2009, 9, 921–937.

Pindelska, E. Sokal, A. and Kolodziejski, W. Pharmaceutical Cocrystals, Slats and Polymorphs: Advanced Characterization Techniques. Adv. Drug Deliv. Rev. 2017, 1, 111–146.

Kotak U, Prajapati VD, Solanki HK, Jani GK, Jha P. Cocrystallization Technique Its Rationale and Recent Progress.World J Pharm Pharm Sci 2015; 4(4): 1484-508.

Yao H. and Kimura K. Field Emission Scanning Electron Microscopy For Structural Characterization of 3d Gold Nanoparticle Superlattices. In: Méndez-Vilas A, Díaz J, eds. Modern Research and Educational Topics in Microscopy. Formatex; 2007. p. 568-75.

Almarsson Ö., Peterson M. L. and Zaworotko M. The A to Z of Pharmaceutical Cocrystals: A Decade of Fast-moving New Science and Patents. *Pharm Pat Anal*. 2012; 1(3): 313-327. doi:10.4155/ppa.12.29

EMA, Eur. Med. Agency, 2015, vol. 44, pp. 1–10.

Amos J. G., Indelicato J. M., Pasini C. E. and Reutzel S. M. Complexes of Cephalosporins and Carbacephalosporins with Parabens. US Patent 6001996A. Eli Lilly and Co Ltd (GB); 1995.

Remenar J., MacPhee M., Peterson M., Morissette S. and Almarsson O. Crystalline Forms of Conazoles and Methods of Making and Using the Same. US Patent 7446107. TransForm Pharmaceuticals Inc; 2002.

Sependa G. J. and Storey R. AZD1152; a Phosphate Prodrug and Maleic Acid Cocrystal. US Patent 7625910. Astra Zeneca AB.

Oliveira M. and Peterson M. Mixed Cocrystals and Pharmaceutical Compositions Comprising the Same. EU Patent 1755388B1. TransForm Pharmaceuticals, Inc.

Zhang Y., Connelly P. R. and Johnston S. Co-crystals and Pharmaceutical Compositions Comprising the Same. EU Patent 2185546B1. Vertex Pharmaceuticals, Inc; 2011.

Mascitti V. and Collman B. M. Dioxa-bicyclo[3.2.1.]octane-2,3,4-triol Derivatives. EU Patent 2334687B1. Pfizer Inc.

Imamura M., Nakanishi K., Shiraki R., Onda K., Sasuga D. and Yuda M. Cocrystal of C-glycoside derivative and L-proline. US Patent 8097592. Astellas Pharma Inc./Kotobuki Pharmaceutical Co. Ltd; 2006.

Ingelheim Pharma Gmbh & Co. Kg Boehringer, Betageri R, Bosanac T, Burke MJ, Harcken C, Kim S, *et al*. Glucocorticoid Mimetics, Methods of Making them, Pharmaceutical Compositions, and Uses thereof. EU Patent 2300472B1. Boehringer Ingelheim Intl. GmBH.

Grunenberg A., Queckenberg K. F., Reute C., Keil B., Gushurst K. S. and Still E. J. New co-crystal Compound of Rivaroxaban and Malonic Acid. EU Patent 2288606B1. Bayer Pharma Ag.

Hanna M., Shan N., Cheney M. L. and Weyna D. R. In Vivo Studies of Crystalline Forms of Meloxicam. US Patent 8124603. Grunenthal GmbH/Thar Pharmaceuticals; 2008.

Childs S. L. Metronidazole Cocrystals and Imipramine Cocrystals. US Patent 8163790. New Form Pharmaceuticals, Inc; 2006.

Grisenti P., Argese M., Scrocchi R., Livieri A. and Guazzi G. Crystalline Form of Tiotropium Bromide With Lactose. US Patent 20170044176 A1. Euticals Spa; 2014.

Tan J. and Shytle R. D. Ionic Cocrystal of Lithium, Lispro, For the Treatment of Fragile X Syndrome. US Patent 20170224724 A1. University of South Florida; 2016.

Albert E., Andres P., Bevill M. J., Smit J. and Nelson J. Cocrystals of Progesterone. US Patent 20170101433 A1. AMRI SSCI LLC; 2012.