A review of novelistic method used for formation pharmaceutical Cocrystals and Marketed available formulation

Manish Kumar Saxena*, Kaushal Kumar, Sobhna Singh

Faculty of Pharmacy, M.J.P Rohilkhand University, Bareilly, India

Corresponding author: **Manish Kumar Saxena**

Abstract

Pharmaceutical cocrystallization is a potential method for improving the solubility of BCS Classes II & IV drugs that are poorly soluble. The majority of scientists are ignorant of this method and the advantages of cocrystallization on the stability and pace of drug dissolution. **Approach:** Evidence was systematically and concisely gathered from a variety of publications using Medline, Pubmed, Embase, Scopus, Google Scholar, and Web of Science. This study covers cocrystallization technologies, goods that have been sold using this approach, and issues related to these procedures. **Finding:** The novelistic or current techniques used for the production of cocrystals are hot melt extrusion, spray evaporation, super critical fluid dynamic technology and laser irradiation which is the most trending and effective method for cocrystal formation. This paper also includes the various in-vitro evaluation parameters that are carried out for evaluating the cocrystals and their drug release. It also defines the reasons for the interest of cocrystals by a researcher and pharmaceutical industries, various novelistic and traditional method of manufacturing of pharmaceutical cocrystal. **Conclusion:** Pharmaceutical crystals are now seen as a significant medicinal or research need. This is evident in the numerous reviews and research papers that have been published in different publications over the previous ten years. Various pharmaceutical businesses have been enforcing patents internationally in recent years. These businesses are expanding quickly as a result of the legislation and intellectual property connection. Pharmaceutical crystals are a crucial and effective method for increasing a drug's bioavailability, stability, and melting point.

Key Words: 1.Coformer, 2.physicochemical properties, 3.preformulation, 4.cocrystals.

1. Introduction

The main factor to determine the efficacy and activity of active chemical moiety is solubility and its dissolution rate [1]. In this current era, cocrystals are on the great interest of the researchers due to its best and tremendous improvement in physicochemical properties of drug substances [2]. Traditional way of drug discovery was based on serendipitous discoveries or traditional remedies. Over the last two decades, however, insist on having a rational design and conglomerate of drug(s) resulting in the emergence of development of drug candidates [3]. For the efficacy, numerous of new drug targeting methods have been developed. Potential drug molecules have been synthesized and modern techniques have been used like combinatorial chemistry and High-Throughput Screening (HTS) for development of better drug molecule [3,4]. US FDA (Food and Drug Administration) defines the cocrystals as a crystalline substance made up of couple or more non-identical molecules, emblematically drug substance and crystal formers or co-formers, in the similar crystal lattice [5,6]. Even after the definition by USFDA, accurate definition of cocrystal is still in discussion. For manufacturing of cocrystals, drug substance and co-formers are taken in stoichiometric ratio (resultant is equal to the sum of moles of drug substance and co-formers) [7,8,9]. The textbook written by the Paul Pfeiffer defines the cocrystals and divide them on the basis of their source of origin into two categories which are; Cocrystals that are made up of inorganic: organic component while the other one is made up of only organic components. Organic: Inorganic means co-former can be organic or active moiety and vice versa. While in another type, both co-former and API should be organic only. In ambient condition, co-crystals are found to be in a solid state and they are the multicomponent compounds formed within the surrounding of molecular or charged active ingredient (Fig.1) [10]. Now a days,

industrial R&D (Research & Development) scientists are working on the formulation of drug using cocrystal techniques to enhance or improve the aqueous solubility of class II type of drug in BCS classification, as this class of drug have low solubility but high permeability [11,12].

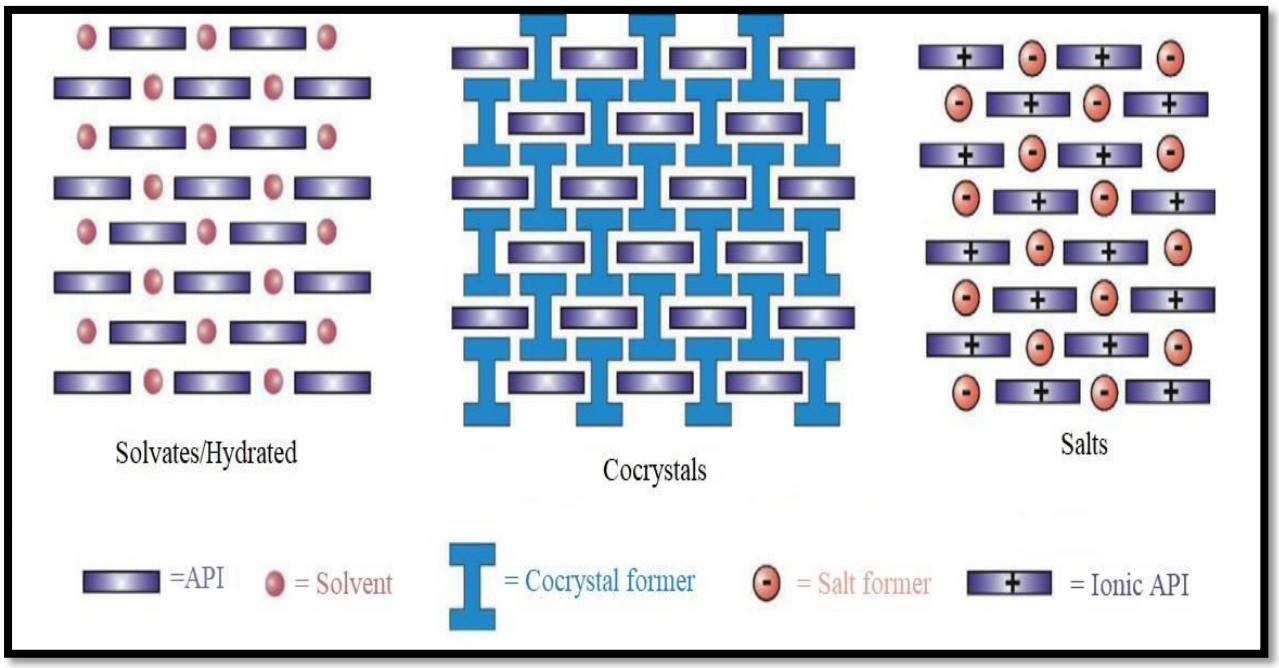

Figure 1: Schematic Representation of Hydrates/Solvates, Cocrystal and Salts

2. Cocrystal drugs that are available in market

The recently approved drug that is available in market is E-58425, which is a combination of two drug Tramadol and Celecoxib and developed by the company with name Esteve Pharmaceutical and it is used in treating the acute pain that are associated due to Osteo Arthritis and gout [5]. Another drug that was approved by FDA in 2015 was Entresto, which is a combination of Sacubitril Sodium and Valsartan Sodium [13]. Valsartan used in this formulation blocks the Angiotensin receptor that is type I (AT1), while Sacubitril is a metabolite of prodrug. This cocrystal formulation helps in preventing various types of heart failure and gives the time to heart patient for surviving without any damage to the heart [14]. Another drug that is used widely in present for the cure of vertigo or motion sickness is Dimenhydrinate [15], which is synthesized by combining Diphenhydramine and 8-chlorotheophylline. As we know diphenhydramine is having antihistamine effect as well as slight anti cholinergic effect and 8-chlorotheophylline is used to remove the drawbacks of drowsiness associated with antihistaminic activity, which in combination helps in prevention of nausea, vomiting and motion sickness or vertigo [16].

One of the best medicines that is available in market and widely used due to best effect is Depakote [17]. Valproic acid and Sodium Valproate is the combination of this drug and used for the treatment of slight depression, seizure and epilepsy. Aqueous solubility of valproic acid is very poor but co-crystallization technique/method improves its physicochemical properties and reduces its side-effects. Valproic acid show its effect/pharmacological action in many ways, like by inhibiting histone deacetylase, direct acting on aminobutyric acid level in CNS and also blocks the voltage-gated ion channel [18].

Widely used muscle relaxant that is in the form of cocrystal is Dichloralphenazone, this formulation is a combination of NSAIDs i.e. Antipyrine and chloral hydrate in 1:2. Antipyrine is COX inhibitor and inhibits all COX-1, COX-2, COX-3 enzymes responsible for the synthesis of prostaglandin. This combination drug is used in the treatment or prevention of headache associated with migraine or tension [19].

S.NO.	Marketed Name	Composition of Drug	Pharmacological Uses
1	Dimenhydrinate	Diphenhydramine + 8-chlorotheophylline	Motion Sickness, Nausea, Vomiting.
2	Depakote	Sodium Valproate + Valproic Acid	Epilepsy & Bipolar Disorder And to prevent Migraine Headache
3	E-58425	Tramadol (44mg) + Celecoxib (56mg)	Acute Pain
4	Dichloralphenazone	Antipyrine + Chloral Hydrate (1:2)	Migraine And Tension Associated Headache
5	Entresto	Sacubitril (49mg) + Valsartan (51mg)	Treat certain type of heart failure (Angiotensin Receptor Blocker)

Table 1: List of drug-drug cocrystals that are available in market

3. Method of preparation of cocrystals

The mechanism of cocrystal formation is not well understood. A recent study utilizing solid-state NMR for characterization suggests that the intermediate formation of the amorphous phase and then its transition to a crystalline state like polymorphs does occur in the case of cocrystals. Since the mechanism of cocrystal formation is not fully clear, co-crystallization methods remain empirical and more or less the same methods are adopted for co-crystallization as for polymorphic crystal formation [20]. Cocrystals are generally prepared by slow solvent evaporation but this is only possible when there exist compatible solubilities of both the components in a given solvent resulting in potential co-crystal. Blagden et al have reported potential benefits as well as disadvantages and methods of preparation of cocrystals. Among these, the solvent drop grinding method has presented itself to be a reliable, environment-friendly and economical method of cocrystals production and in the discovery of new cocrystals. The slurry crystallization technique has been used with equal importance in a co-crystal screening of nonionizable pharmaceutical. Hydrogen bonding and geometric fit play significant roles in cocrystal formation [21].

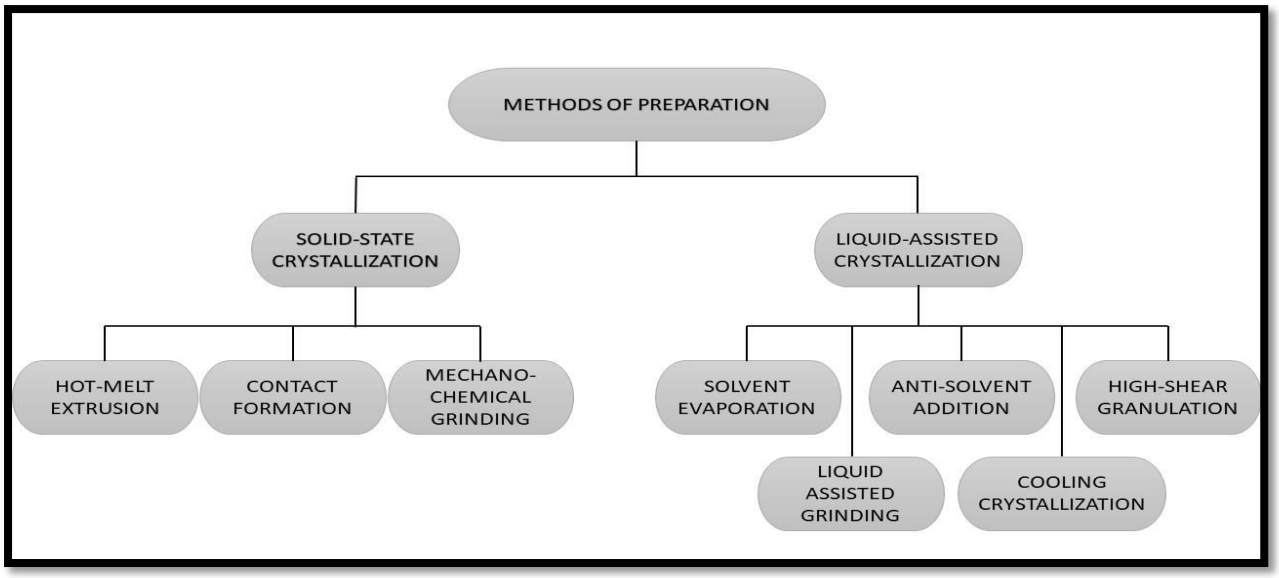

Figure 2: Method of preparation of cocrystals

3.1. Formation of cocrystals via solid state method

Solid state method used for the production of pharmaceutical cocrystals attracted interest of many researchers from past few years due to its tremendous advantages occurred by these processes. First time, this solid-state grinding was reported in late 19th century. This idea was proceeded to addition of solvent which was further established to enhance the kinetics and facilitate cocrystal development. Due to no use of solvent or negligible amount of solvent used provides an excellent quality with best purity. This method of manufacturing cocrystals need less time with high throughput as compared to any other type. All methods that are used under solid state cocrystal formation are discussed below with its implementation as well as pros and cons [22-24].

a. Hot Melt Extrusion (HME) for cocrystal production

HME is a method or process of obtaining product of uniform shape and size which is initiated by the conveying of raw material with the help of rotating screw under specific temperature [25]. Hot melt extrusion (HME) method is a leading-edge technology that has been used for the development of pharmaceutical cocrystals by using heat to melt the conformer and drug substance. Few years back, hot melt extrusion method was used for the production of plastics and food item but now in this era, it was found to be the best method for the production of pharmaceutical dosage form [26].

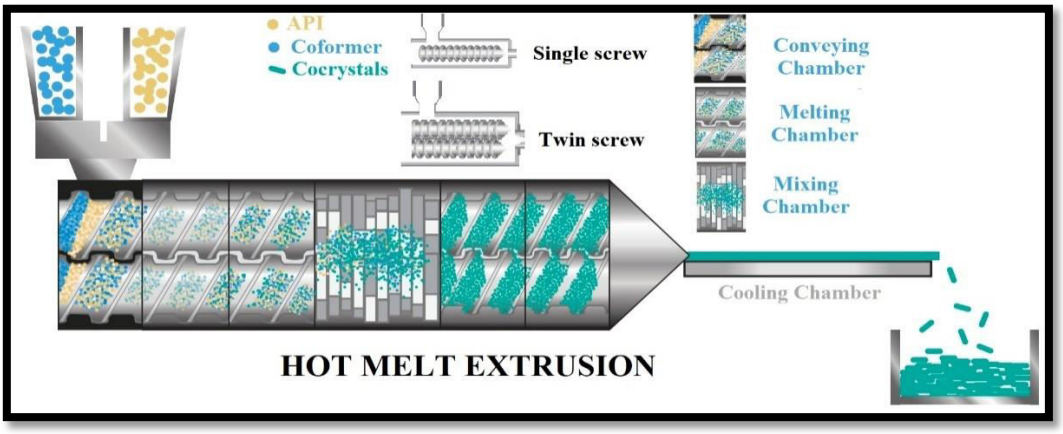

Figure 3: Hot melt extrusion apparatus

b. Contact formation

When API and conformer are mixed under controlled atmospheric environment, the cocrystals are spontaneously formed. No mechanical force is required. In some of the cases, grinding of pure components occur [27].

At high temperature and relative humidity, the rate increased. Ibrahim et al. reported that smaller the particle size distribution, more will be the cocrystal formation as they mentioned i.e., between 20 to 45 u_m.[28]

Mechanism of cocrystalization in moisture have 3 deliquescent stages:

- Moisture uptake
- Dissolution of reactant
- Cocrystal nucleation and growth

In this method, one component is melted and solidified. The other component is allowed to contact with the first melted component. After recrystallization, a zone of mixing is created then compare these with binary diagram of two components and by this they are able to identify formation of Nicotinamide-ibuprofen, nicotinamide-salicyclic acid, Nicotinamide-flubiprofen, and nicotinamide-fenfeim. [29,30]

c. Dry/Neat Grinding

This method of cocrystallization involves the combination of pharmacological active molecule (API) and conformer in their solid and dry state and pressure is applied on them manually (mortar-pestle) or mechanically (automated ball mill) [31].

The starting solid material should not be melted during grinding, otherwise it is called melt crystallization. The temperature is also monitored so that the material should not be melted [32].

Benefit of solid state grinding over solution-based method is that it does not loose the yield in solvent due to the solubility [33].

Issue related to the dry grinding are:

- **Failure to form a cocrystal.**
- **Incomplete conversion to the crystal:** Excess starting material is rendered in the product. Due to this, the incomplete conversion to cocrystal may occur that is undesirable because it increases the purification step to yield a pure cocrystal product. Increased grinding time can resolve this problem but nonstoichiometric cocrystal formation can take place [34].
- **If some amorphous content formed in, then the possibility of crystalline defects may occur.** Dry grinding should be completed using molar equivalent and excess of each starting material. This can lead to favorite discovery of alternate cocrystal if exit for a system. [35]

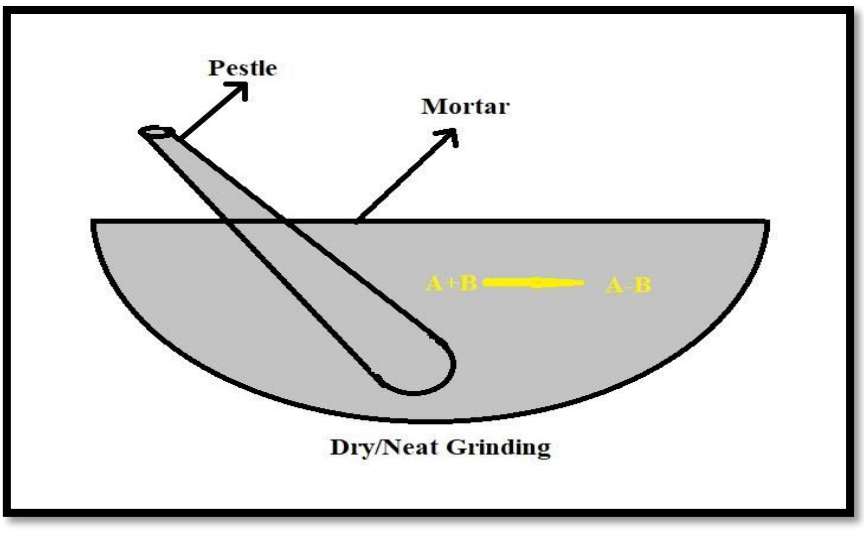

Figure 4: Dry/Neat Grinding

3.2.Formation of cocrystal via solution-based method

a. Evaporation cocrystallization

In solvent evaporation method, drug and coformer are dissolved in solvent having higher solubility of drug and then solvent is evaporated in hot air oven leading to formation of cocrystals [36].

The mixture of both coformer in a solvent first involve nucleation and growth, then supersaturation by evaporation of the solvent. Small no. of large cocrystals were formed by shear evaporation. The necessary step for the discovery of new cocrystal form is identification [37].
By identification, it should be defined that whether the obtained crystal is a cocrystal, salt, hydrate or anyother polymorphic form of API or coformer.
More attention is not given to the solvent in evaporative cocrystallization. Depending on the solvent volatility, evaporation cocrystallization can be very slow-evaporative that can also take upto 6 months. Elevated temperature is used to accelerate the rate of evaporation, but very high temperature during evaporation may lead to the change in pharmacological action of drug used in formation of cocrystal. [38]

b. Cooling crystallization

In a reactor jacketed vessel, large amount of reactant and solvent are mixed. The mixture is heated at high temperature to make sure all solutes get totally dissolved in solvent followed by cooling [39].
As the temperature drops, the super saturation takes place with respect to the crystal and crystal will precipitate. Through the analysis of lattice pathway and supersaturation level of component, the optimal operation conditions for cooling crystallization process can be found. [40,41]

c. Antisolvent cocrystallization

Another name of antisolvent addition method is “vapor diffusion” in which anti solvent is used for obtaining good quality of cocrystals. In this method, compound having less solubility to the solvent is added to the solvent having good solubility which favors the precipitation of drug-coformer[42,43].
Generally, during the process of cocrystallization, supersaturation is obtained by adding the solvent having low or no solubility to the solution of drug and conformer at specific temperature and controlled RPM over magnetic stirrer. The change in temperature and constant stirring leads to the formation of cocrystals. The solvent having no solubility to drug and coformer is cooled to 3^{o}C over ice bath while the antisolvent is heated to 45^{o}C. On addition of both the solvents, stirring is required that is facilitated by using magnetic stirrer. [44-47]

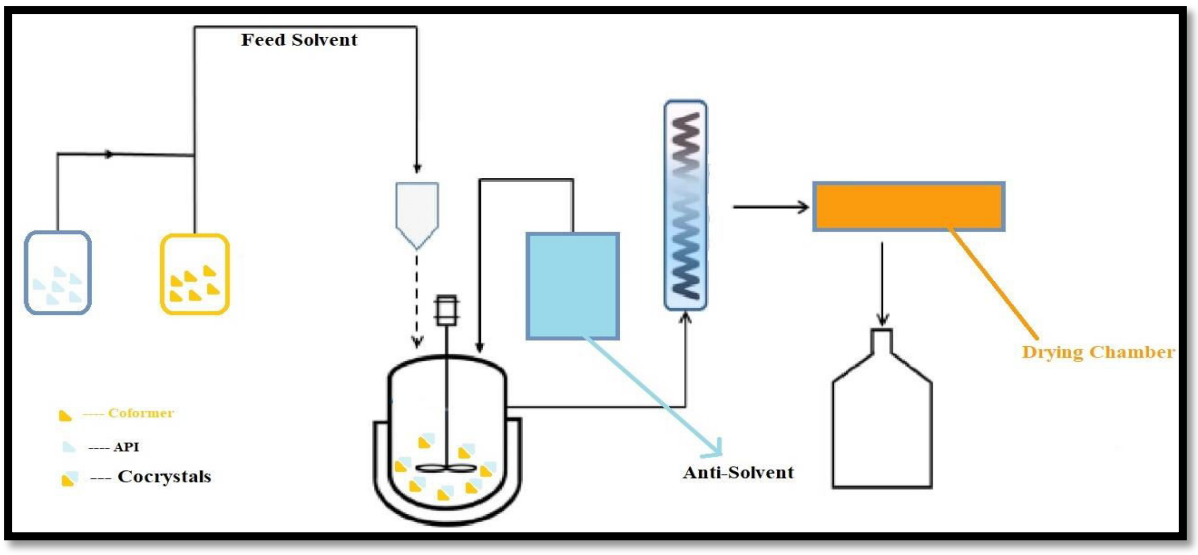

Figure 5: Antisolvent cocrystallization

d. Liquid Assisted Grinding

Before the milling of solid drug, a very small amount of solvent is added in it. The solvent should persist during the grinding process and it has catalytic role in the cocrystal formation [48]. Solvent increases the kinetics of cocrystal formation but at yet this is unresolved. The solvent component increases the reaction kinetics by wetting the solid surface. Benzoic acid crystal was formed by wetting equimolar mixture of benzoic acid and carboxylic acid by adding methanol in mortar [49].

The mixture of caffeine and tetrafluoro succinic acid was grinded at 30 Hz for 30 minutes and 50μl of nitromethane was added to it, the cocrystals formed were 1:1. For generating highly water soluble cocrystal of poorly soluble nutraceutical hesperetin (HESP), the solvent drop grinding cocrystallization method was applied. [50,51]

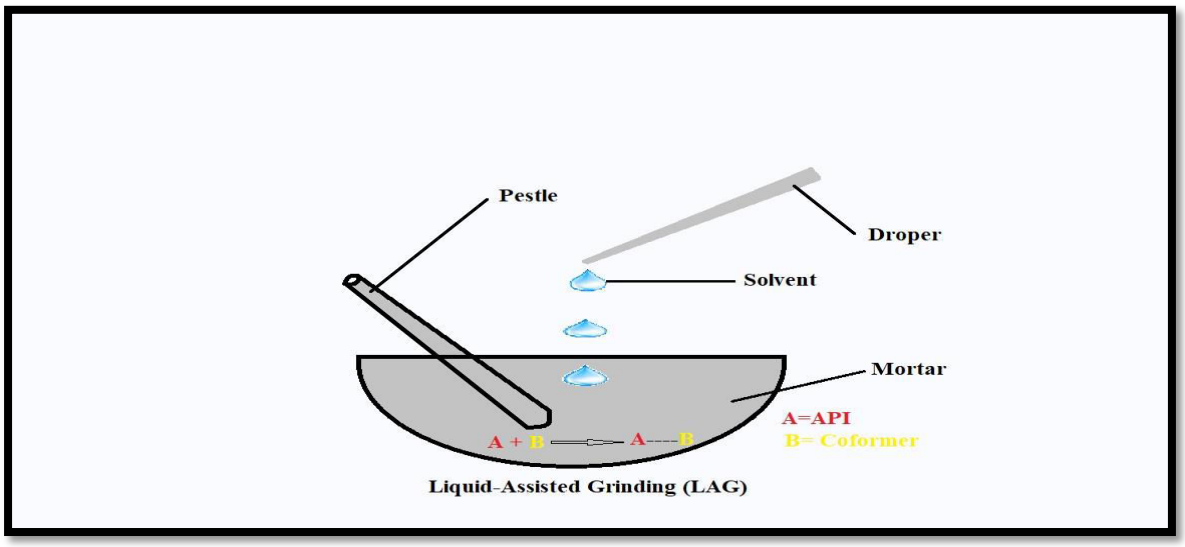

Figure 6: Liquid-Assisted grinding

e. High shear wet granulation

The powder particle agglomerated in the presence of binder via liquisolid medium. High shear granulator is used for this method. With the help of chopper and impellers shear is imparted on the powder mixture. The mechanism of cocrystal formation by this technique is not exactly known but either similar to liquid assisted grinding or slurry transformation. High shear wet granulation is one of the best methods to obtain pharmaceutical cocrystal with highest yield which can minimize the loss of drug and conformer. [52]

4. Techniques used for characterization of cocrystals

- ***Fourier-Transform Infrared Spectroscopy***

The study of the interaction of infrared radiation with materials by absorption, emission, or reflection is known as infrared spectroscopy (also known as IR spectroscopy or vibrational spectroscopy) [53]. Chemical compounds or functional groups in solid, liquid, or gaseous forms are studied and identified using this technique. It can be applied to classify novel materials or locate and authenticate known and unidentified samples. An equipment known as an infrared spectrometer (or spectrophotometer), which generates an infrared spectrum, is used to perform the infrared spectroscopy method or procedure [54]. An IR spectrum can be shown as a graph with the absorbance (or transmittance) of infrared light on the vertical axis and the wavelength, frequency, or wavenumber on the horizontal axis. Reciprocal centimetres, denoted by the sign cm^{-1}, are the most common wavenumber units used in IR spectra. IR wavelength measurements are frequently expressed in terms of micrometres, sometimes known as "microns," with the symbol "m," which have a reciprocal relationship with wavenumber. A Fourier transform infrared (FTIR) spectrometer is a typical laboratory apparatus that makes use of this approach. IR in two dimensions is also conceivable.[55-59]

- ***Solid-State Nuclear Magnetic Resonance***

A spectroscopic method for observing the local magnetic fields surrounding atomic nuclei is nuclear magnetic resonance spectroscopy, also referred to as magnetic resonance spectroscopy (MRS) or NMR spectroscopy [60-63]. The sample is placed in a magnetic field, and the nuclear magnetic resonance (NMR) signal is generated by radio waves excitation of the sample's nuclei, which is detected by sensitive radio receivers. A molecule's intramolecular magnetic field can alter the resonance frequency, providing information about a molecule's electronic structure and its various functional groups. In contemporary organic chemistry, NMR spectroscopy is the only reliable way to identify monomolecular organic molecules since the fields are distinctive or highly specific to particular compounds [64,65].

Three successive processes typically make up the NMR principle:

- the polarisation of magnetic nuclear spins in a magnetic field B0 that is being applied [66].
- the alteration of this nuclear spin alignment caused by a radio-frequency (RF) pulse, a weakly oscillating magnetic field [67].
- detection and analysis of the electromagnetic waves that this disruption causes the sample's nucleus to generate [68].

Similar to this, biochemists utilize NMR to locate complicated compounds like proteins. NMR spectroscopy offers comprehensive details about the structure, dynamics, reaction state, and chemical environment of molecules in addition to molecular identification. Proton and carbon-13 NMR spectroscopy are the most used types of NMR; however, it can be used with any sample that has nuclei with spin.[69,70]

- ***Thermal Gravimetry Method***

The difference in the amount of heat needed to raise the temperature of a sample compared to a reference is assessed as a function of temperature using the differential scanning calorimetry (DSC) thermoanalytical technique. Throughout the experiment, the sample and reference are kept at nearly the same temperature. For a DSC study, the temperature programme is often created so that the sample holder temperature rises linearly with time. Over the range of temperatures to be scanned, the reference sample should have a heat capacity that is well established [71,72].

The difference in heat flux between a sample and a reference is measured by the Heat-flux DSC, one of the two primary forms of DSC (which gives it the alternative name Multi-Cell DSC). Additionally, Power differential DSC evaluates the variance between the power delivered to the sample and a reference [73,74].

DSC is commonly used to measure a variety of properties in both organic and inorganic materials, from metals and simple compounds to polymers and pharmaceuticals. The properties measured include:

Glass transitions
Phase changes
Melting
Crystallization
Product stability
Cure/cure kinetics
Oxidative stability
Heat capacity and heat of fusion measurements etc. [75]

- ***UV Spectroscopy***

In the ultraviolet and the entire, nearby visible parts of the electromagnetic spectrum, absorption spectroscopy or reflectance spectroscopy is referred to as UV spectroscopy or UV-visible spectrophotometry (UV-Vis or UV/Vis) [76]. This methodology is frequently employed in a variety of practical and theoretical applications since it is reasonably affordable and simple to execute. The sample must only be a chromophore and absorb in the UV-Visible range. Fluorescence spectroscopy is enhanced by absorption spectroscopy. Aside from the measurement wavelength, variables of importance include absorbance (A), transmittance (%T), and reflectance (%R), as well as how they change over time [77].

For the quantitative determination of a variety of analytes or samples, including transition metal ions, highly conjugated organic compounds, and biological macromolecules, UV-Vis spectroscopy is frequently utilized in analytical chemistry. Although solids and gases, as well as liquids, can be examined by spectroscopy [78,79].

- ***Hansen Solubility Study***

The Hansen solubility parameters are useful for predicting solvent-solute affinity. Hansen solubility parameter (HSP), which separates the cohesion energy of mixtures into the London dispersion forces, dipole forces, and hydrogen bonding force. HSP value is used for various research fields, such as an evaluation of the solubility of solids in solvent, the compatibility and affinity of polymers in solvent, and the dispersibility of fine particles in solvent. On the other side, one of the methods of HSP for a liquid or its mixture can be measured from the physical properties of the solvent (such as refractive index, surface tension, permittivity, and dipole moment). [80,81]

- ***dissolution study***

Dissolution testing is an essential analytical procedure that's required as part of the final release investigation for solid oral dosage forms to control product quality, stability, and batch-to-batch consistency. [82,83]
Because oral solid dosage forms are still the most common way in which drugs are administered, dissolution of the dosage form after it is swallowed, namely the rate at which the active ingredient is released into the body, is a critical facet of drug development. "Dissolution testing is an essential analytical procedure that's required as part of the final release investigation for solid oral dosage forms to control product quality, stability, and batch-to-batch consistency". As the rate of dissolution can significantly affect bioavailability, the goal of dissolution tests and associated acceptance criteria should be to identify batches with unacceptable bioavailability. [84]
The primary function of a dissolution test during the early stages of development is to characterize therapeutic efficacy, bioequivalence, and bioavailability of API. During later stages of the development process, dissolution testing is also used for quality control. A dissolution test uses an apparatus with specific test conditions in combination with the acceptance criteria to evaluate the performance of the product. [85,86]

- ***stability Study***

As it recognizes the various climatic storage conditions and half-life of the medicine or products connected to the drug, it is one of the persuasive parameters for the evaluation of the co-crystals. The investigation is conducted for a predetermined amount of time at a specific temperature and humidity level in order to estimate the half-life of the co-crystals and products under various storage circumstances. Other factors that affect the stability of pharmaceuticals, such as humidity, light, and temperature, are also taken into account.
Pharmaceutical companies watch their products during stability testing, which lasts for defined amounts of time to assess if there has been any change over time in particular environmental conditions, quality of the finished product, or active pharmaceutical ingredient (API) (FP). It is done to ascertain whether the quality of the Active Pharmaceutical Ingredient (API) or Final Product has changed over time in a particular environment (FP) or not. Before a pharmaceutical or other FDA-regulated product is approved for sale and distributed to the public for consumption, a number of factors must be assessed. Pharmaceutical producers must be extremely careful to monitor how different environmental elements like light, temperature, and humidity affect their goods [87,88].
Various research should be done on the stability of drugs. The following are the main categories of stability studies:

- Enduring stability
- Middle-ground stability
- Enhanced stability.
- Utilization stability

5. Challenges in developments of pharmaceutical cocrystals

The selection of appropriate conformers presents the main difficulty in the creation of medicinal cocrystals. Since there are theoretically many potential conformers, it is necessary to create a screening instrument that can identify the likely conformers. Following that, these expected conformers should be physically screened to see if cocrystals develop. The past few decades have seen a significant increase in study into cocrystals, and as a

result, enough information has been gathered to forecast the likely conformers [89]. Some successful methods for screening conformers include the hydrogen bond propensity, Cambridge Structural Database, supramolecular synthon approach, pKa rule, and Hansen solubility parameter; however, the successful application of cocrystallization to the pharmaceutical industry depends on the creation of more potent screening tools [90].
Different cocrystallization techniques can be used to filter cocrystals. The use of solvent-based cocrystallization techniques involves a number of difficulties, including picking an appropriate solvent, varying the solubility of the API and conformer (congruent and incongruent), concentration effects, selecting the appropriate heating and chilling profiles, etc[91]. For cocrystal screening, solid-state milling is superior to solvent-based techniques. However, there are instances when phase changes are brought about by solid-state grinding in medicinal cocrystals.The formation of salts, solvates, or hybrids, the inherent instability of cocrystals, the instability of cocrystals in solution phase, i.e., variations in the stability, dissolution profile, and solubility of cocrystals based on pH, ion concentration, and surfactant concentration are among the challenges involved in the synthesis and characterization of cocrystals. The risks of cocrystal dissociation in the formulation due to interactions with formulation ingredients (excipients), the replacement of conformers by excipients, changes to the cocrystal's stoichiometry, and conversion to a less soluble parent drug during dissolution are thus issues that must be addressed during cocrystal preparation [92].

6. Conclusion and future perspective:

Nowon days pharmaceutical cocrystals became an important drug space or research gap. This can be seen in various number of review and research papers publishing in various journals over the past decade. In past few years, various pharmaceutical industries are imposing patents worldwide. These companies are growing rapidly due to its regulation and relationship of intellectual property. Pharmaceutical cocrystal is the important and excellent tool to enhance the bioavailability, stability and also improving the melting point of a drug that belongs to BCS Class II & IV. Selection of coformers and solvents is the main challenge in preparation of cocrystals.
In this review, we discussed in detail about the wide range of technologies used in testing, compilation and production of cocrystals in the pharmacy to overcome physical weakness API properties. This understanding of the review is provided in the proposed methods of cocrystallization to be developed with different techniques. During early development, the processes of cocrystallization were very focused on traditional methods, such as solvent-solvent, grinding and slurry method. However, as time has passed and the field has advanced, scientists in this field have come up with new ways of saying they become increasingly easy to empower cocrystallization processes to overcome the past limitations. Nuclear methods that can be used for cocrystallization are hot melt extrusion, spray drying, supercritical fluid technology, laser irradiation, freeze-dry, microfluidic and jet dispensing, etc.
These methods successfully form different types of cocrystals that make up the drug. However, all of the methods still need to be carefully investigated to better understand the obvious the cocrystallization method for each method. It is very evident in the amount of interest shown by both academics and medical professional industry that soon drug cocrystals will become one of the strongest and most important type of medicines. Cocrystals can be used in the following fields:

- Reconstruction of existing medicines to improve their effectiveness.
- Health cycle management with newly approved drugs.
- Facilitate compilation of development novels; operation and cleaning.
- Raw chemistry and integration with cocrystals as intermediates.

7. References:

1. Dalpiaz, A., Pavan, B., & Ferretti, V. (2017). Can pharmaceutical co-crystals provide an opportunity to modify the biological properties of drugs?. *Drug Discovery Today*, *22*(8), 1134-1138.

2. S Panzade, P., & R Shendarkar, G. (2017). Pharmaceutical cocrystal: an antique and multifaceted approach. *Current drug delivery*, *14*(8), 1097-1105.

3. Buddhadev, S. S., &Garala, K. C. (2021). Pharmaceutical cocrystals—a review. *Multidisciplinary Digital Publishing Institute Proceedings*, *62*(1), 14.
4. Chopra, V., & Joseph, A. (2019). Synthesizing Cocrystals: A Brief Overview on Cocrystals and its Rapid Screening. *Think India Journal*, *22*(37), 124-133.

5. Shinozaki, T., Ono, M., Higashi, K., &Moribe, K. (2019). A novel drug-drug cocrystal of levofloxacin and metacetamol: Reduced hygroscopicity and improved photostability of levofloxacin. *Journal of Pharmaceutical Sciences*, *108*(7), 2383-2390.

6. Kulkarni, A., Bachhav, R., Hol, V., &Shete, S. (2020). Co-crystals of active pharmaceutical ingredient-ibuprofen lysine. *Int. J. Appl. Pharm*, *12*, 22-32.

7. Yin, H. M., Wu, N., Zhou, B. J., Hong, M. H., Zhu, B., Qi, M. H., & Ren, G. B. (2020). Slow-release drug–drug cocrystals of oxaliplatin with flavonoids: delaying hydrolysis and reducing toxicity. *Crystal Growth & Design*, *21*(1), 75-85.
8. Eesam, S., Bhandaru, J. S., Akkinepally, R. R., &Bobbala, R. K. (2021). Cocrystallization of gliclazide with improved physicochemical properties. *Future Journal of Pharmaceutical Sciences*, *7*(1), 124.

9. Mithu, M. S. H., Ross, S. A., Hurt, A. P., &Douroumis, D. (2021). Effect of mechanochemical grinding conditions on the formation of pharmaceutical cocrystals and co-amorphous solid forms of ketoconazole–Dicarboxylic acid. *Journal of Drug Delivery Science and Technology*, *63*, 1-11.

10. Bennion, J. C., &Matzger, A. J. (2021). Development and evolution of energetic cocrystals. *Accounts of Chemical Research*, *54*(7), 1699-1710.

11. Bolla, G., &Nangia, A. (2016). Pharmaceutical cocrystals: walking the talk. *Chemical communications*, *52*(54), 8342-8360.

12. Vishweshwar, P., McMahon, J. A., Bis, J. A., &Zaworotko, M. J. (2006). Pharmaceutical co-crystals. *Journal of pharmaceutical sciences*, *95*(3), 499-516.

13. Sauer, A. J., Cole, R., Jensen, B. C., Pal, J., Sharma, N., Yehya, A., & Vader, J. (2019). Practical guidance on the use of sacubitril/valsartan for heart failure. *Heart failure reviews*, *24*, 167-176.

14. Guo, M., Sun, X., Chen, J., & Cai, T. (2021). Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharmaceutica Sinica B*, *11*(8), 2537-2564.

15. Ehling, S., Bäumer, W., &Papich, M. G. (2019). Diphenhydramine pharmacokinetics after oral and intravenous administration of diphenhydramine and oral administration of dimenhydrinate to healthy dogs, and pharmacodynamic effect on histamine-induced wheal formation: a pilot study. *Veterinary dermatology*, *30*(2), 91-e24.

16. Cheney, M. L., Weyna, D. R., Shan, N., Hanna, M., Wojtas, L., &Zaworotko, M. J. (2011). Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics. *Journal of pharmaceutical sciences*, *100*(6), 2172-2181.
17. Codagnone, M. G., Podestá, M. F., Uccelli, N. A., &Reinés, A. (2015). Differential local connectivity and neuroinflammation profiles in the medial prefrontal cortex and hippocampus in the valproic acid rat model of autism. *Developmental neuroscience*, *37*(3), 215-231.
18. Kale, D. P., Zode, S. S., & Bansal, A. K. (2017). Challenges in translational development of pharmaceutical cocrystals. *Journal of Pharmaceutical Sciences*, *106*(2), 457-470.
19. Aupanun, S., Laus, F., Poapolathep, A., Owen, H., Vullo, C., Faillace, V., & Giorgi, M. (2016). Pharmacokinetic assessment of the marker active metabolites 4-Methyl-amino-antipyrine and 4-Acetyl-amino-

antipyrine after intravenous and intramuscular injection of metamizole (Dipyrone) in healthy donkeys. *Journal of Equine Veterinary Science*, *47*, 55-61.

20. Rodrigues, M., Baptista, B., Lopes, J. A., &Sarraguça, M. C. (2018). Pharmaceutical cocrystallization techniques. Advances and challenges. *International Journal of Pharmaceutics*, *547*(1-2), 404-420.
21. Malamatari, M., Ross, S. A., Douroumis, D., &Velaga, S. P. (2017). Experimental cocrystal screening and solution based scale-up cocrystallization methods. *Advanced drug delivery reviews*, *117*, 162-177.
22. Douroumis, D., Ross, S. A., &Nokhodchi, A. (2017). Advanced methodologies for cocrystal synthesis. *Advanced drug delivery reviews*, *117*, 178-195.
23. Karimi-Jafari, M., Padrela, L., Walker, G. M., & Croker, D. M. (2018). Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. *Crystal Growth & Design*, *18*(10), 6370-6387.
24. Dhumal, R. S., Kelly, A. L., York, P., Coates, P. D., &Paradkar, A. (2010). Cocrystalization and simultaneous agglomeration using hot melt extrusion. *Pharmaceutical research*, *27*, 2725-2733.
25. Gajda, M., Nartowski, K. P., Pluta, J., &Karolewicz, B. (2019). Continuous, one-step synthesis of pharmaceutical cocrystals via hot melt extrusion from neat to matrix-assisted processing–State of the art. *International Journal of Pharmaceutics*, *558*, 426-440.
26. Yadav, B. K., Khursheed, A. T. I. F., & Singh, R. D. (2019). Cocrystals: A complete review on conventional and novel methods of its formation and its evaluation. *Asian J. Pharm. Clin. Res*, *12*(7), 68-74.
27. Schultheiss, N., & Newman, A. (2009). Pharmaceutical cocrystals and their physicochemical properties. *Crystal growth and design*, *9*(6), 2950-2967.
28. Wang, X., Du, S., Zhang, R., Jia, X., Yang, T., & Zhang, X. (2021). Drug-drug cocrystals: opportunities and challenges. *Asian journal of pharmaceutical sciences*, *16*(3), 307-317.
29. Kumar, S. (2018). Pharmaceutical cocrystals: an overview. *Indian Journal of Pharmaceutical Sciences*, *79*(6), 858-871.
30. Patil, A. O., Curtin, D. Y., & Paul, I. C. (1984). Interconversion by hydrogen transfer of unsymmetrically substituted quinhydrones in the solid state. Crystal structure of the 1: 2 complex of 2, 5-dimethylquinone with hydroquinone. *Journal of the American Chemical Society*, *106*(14), 4010-4015.
31. Etter, M. C., &Reutzel, S. M. (1991). Hydrogen bond directed cocrystallization and molecular recognition properties of acyclic imides. *Journal of the American Chemical Society*, *113*(7), 2586-2598.
32. Rodrigues, M., Baptista, B., Lopes, J. A., &Sarraguça, M. C. (2018). Pharmaceutical cocrystallization techniques. Advances and challenges. *International Journal of Pharmaceutics*, *547*(1-2), 404-420.
33. Yadav, A. R., & Mohite, S. K. (2020). Different techniques and characterization of polymorphism with their evaluation: A Review. *Asian Journal of Pharmacy and Technology*, *10*(3), 213-216.
34. Tan, J., Liu, J., & Ran, L. (2021). A review of pharmaceutical nano-cocrystals: A novel strategy to improve the chemical and physical properties for poorly soluble drugs. *Crystals*, *11*(5), 463.
35. Pawar, N., Saha, A., Nandan, N., &Parambil, J. V. (2021). Solution cocrystallization: A scalable approach for cocrystal production. *Crystals*, *11*(3), 303.
36. Douroumis, D., Ross, S. A., &Nokhodchi, A. (2017). Advanced methodologies for cocrystal synthesis. *Advanced drug delivery reviews*, *117*, 178-195.
37. Loschen, C., &Klamt, A. (2015). Solubility prediction, solvate and cocrystal screening as tools for rational crystal engineering. *Journal of Pharmacy and Pharmacology*, *67*(6), 803-811.
38. Thakuria, R., & Sarma, B. (2018). Drug-drug and drug-nutraceutical cocrystal/salt as alternative medicine for combination therapy: a crystal engineering approach. *Crystals*, *8*(2), 101.
39. Lee, M. J., Chun, N. H., Wang, I. C., Liu, J. J., Jeong, M. Y., & Choi, G. J. (2013). Understanding the formation of indomethacin–saccharin cocrystals by anti-solvent crystallization. *Crystal growth & design*, *13*(5), 2067-2074.
40. Chun, N. H., Lee, M. J., Song, G. H., Chang, K. Y., Kim, C. S., & Choi, G. J. (2014). Combined anti-solvent and cooling method of manufacturing indomethacin–saccharin (IMC–SAC) co-crystal powders. *Journal of crystal growth*, *408*, 112-118.

41. Lee, M. J., Chun, N. H., Kim, M. J., Kim, P., Song, K. H., & Choi, G. J. (2015). In situ monitoring of antisolvent cocrystallization by combining near-infrared and Raman spectroscopies. *Crystal Growth & Design*, *15*(9), 4385-4393.
42. Wang, I. C., Lee, M. J., Sim, S. J., Kim, W. S., Chun, N. H., & Choi, G. J. (2013). Anti-solvent co-crystallization of carbamazepine and saccharin. *International journal of pharmaceutics*, *450*(1-2), 311-322.
43. Wang, I. C., Lee, M. J., Sim, S. J., Kim, W. S., Chun, N. H., & Choi, G. J. (2013). Anti-solvent co-crystallization of carbamazepine and saccharin. *International journal of pharmaceutics*, *450*(1-2), 311-322.
44. Padrela, L., de Azevedo, E. G., &Velaga, S. P. (2012). Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. *Drug development and industrial pharmacy*, *38*(8), 923-929.
45. Ross, S. A., Lamprou, D. A., &Douroumis, D. (2016). Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies. *Chemical Communications*, *52*(57), 8772-8786.
46. Braga, D., Giaffreda, S. L., Rubini, K., Grepioni, F., Chierotti, M. R., &Gobetto, R. (2007). Making crystals from crystals: three solvent-free routes to the hydrogen bonded co-crystal between 1, 1′-di-pyridyl-ferrocene and anthranilic acid. *CrystEngComm*, *9*(1), 39-45.
47. Childs, S. L., & Hardcastle, K. I. (2007). Cocrystals of piroxicam with carboxylic acids. *Crystal Growth & Design*, *7*(7), 1291-1304.
48. Karki, S., Fábián, L., Friščić, T., & Jones, W. (2007). Powder X-ray diffraction as an emerging method to structurally characterize organic solids. *Organic letters*, *9*(16), 3133-3136.
49. Rehder, S., Christensen, N. P. A., Rantanen, J., Rades, T., & Leopold, C. S. (2013). High-shear granulation as a manufacturing method for cocrystal granules. *European Journal of Pharmaceutics and Biopharmaceutics*, *85*(3), 1019-1030.
50. Rehder, S., Klukkert, M., Löbmann, K. A., Strachan, C. J., Sakmann, A., Gordon, K., ... & Leopold, C. S. (2011). Investigation of the formation process of two piracetam cocrystals during grinding. *Pharmaceutics*, *3*(4), 706-722.
51. Heiden, S., Tröbs, L., Wenzel, K. J., &Emmerling, F. (2012). Mechanochemical synthesis and structural characterisation of a theophylline-benzoic acid cocrystal (1: 1). *CrystEngComm*, *14*(16), 5128-5129.
52. Sathisaran, I., & Dalvi, S. V. (2018). Engineering cocrystals of poorly water-soluble drugs to enhance dissolution in aqueous medium. *Pharmaceutics*, *10*(3), 108.
53. Jones, W., & Eddleston, M. D. (2014). Introductory Lecture: Mechanochemistry, a versatile synthesis strategy for new materials. *Faraday discussions*, *170*, 9-34.
54. Sopyan, I., Fudholi, A., Muchtaridi, M., &Puspitasari, I. (2016). A Novel of Cocrystalization to Improve Solubility and Dissolution rate of Simvastatin. *Int J PharmTech Res*, *9*(6), 483-491.
55. Deng, J. H., Lu, T. B., Sun, C. C., & Chen, J. M. (2017). Dapagliflozin-citric acid cocrystal showing better solid state properties than dapagliflozin. *European Journal of Pharmaceutical Sciences*, *104*, 255-261.
56. Sopyan, I., Fudholi, A., Muchtaridi, M., & Sari, I. P. (2017). Co-crystallization: a tool to enhance solubility and dissolution rate of simvastatin. *Journal of Young Pharmacists*, *9*(2), 183.
57. Marion, D. (2013). An introduction to biological NMR spectroscopy. *Molecular & Cellular Proteomics*, *12*(11), 3006-3025.
58. Holzgrabe, U. (2010). Quantitative NMR spectroscopy in pharmaceutical applications. *Progress in Nuclear Magnetic Resonance Spectroscopy*, *57*(2), 229-240.
59. Bharti, S. K., & Roy, R. (2012). Quantitative 1H NMR spectroscopy. *TrAC Trends in Analytical Chemistry*, *35*, 5-26.
60. Holzgrabe, U., Deubner, R., Schollmayer, C., & Waibel, B. (2005). Quantitative NMR spectroscopy—applications in drug analysis. *Journal of pharmaceutical and biomedical analysis*, *38*(5), 806-812.
61. Fan, T. W. M., & Lane, A. N. (2016). Applications of NMR spectroscopy to systems biochemistry. *Progress in nuclear magnetic resonance spectroscopy*, *92*, 18-53.
62. Holzgrabe, U., Diehl, B. W., & Wawer, I. (1998). NMR spectroscopy in pharmacy. *Journal of pharmaceutical and biomedical analysis*, *17*(4-5), 557-616.

63. Kessler, H., Gehrke, M., &Griesinger, C. (1988). Two-Dimensional NMR Spectroscopy: Background and Overview of the Experiments [New Analytical Methods (36)]. *AngewandteChemie International Edition in English*, *27*(4), 490-536.
64. Evilia, R. F. (2001). Quantitative NMR spectroscopy. *Analytical Letters*, *34*(13), 2227-2236.
65. Reif, B., Ashbrook, S. E., Emsley, L., & Hong, M. (2021). Solid-state NMR spectroscopy. *Nature Reviews Methods Primers*, *1*(1), 2.
66. Elyashberg, M. (2015). Identification and structure elucidation by NMR spectroscopy. *TrAC Trends in Analytical Chemistry*, *69*, 88-97.
67. Summers, M. F. (1988). 113Cd NMR spectroscopy of coordination compounds and proteins. *Coordination chemistry reviews*, *86*, 43-134.
68. Saganowska, P., &Wesolowski, M. (2018). DSC as a screening tool for rapid co-crystal detection in binary mixtures of benzodiazepines with co-formers. *Journal of Thermal Analysis and Calorimetry*, *133*, 785-795.
69. Spink, C. H. (2008). Differential scanning calorimetry. *Methods in cell biology*, *84*, 115-141.
70. Schick, C. (2009). Differential scanning calorimetry (DSC) of semicrystalline polymers. *Analytical and bioanalytical chemistry*, *395*, 1589-1611.
71. Freire, E. (1995). Differential scanning calorimetry. *Protein stability and folding: Theory and practice*, 191-218.
72. Biliaderis, C. G. (1983). Differential scanning calorimetry in food research—a review. *Food Chemistry*, *10*(4), 239-265.
73. Verma, G., & Mishra, M. (2018). Development and optimization of UV-Vis spectroscopy-a review. *World J. Pharm. Res*, *7*(11), 1170-1180.
74. Atole, D. M., & Rajput, H. H. (2018). Ultraviolet spectroscopy and its pharmaceutical applications-a brief review. *Asian J pharm clin res*, *11*(2), 59-66.
75. Verma, G., & Mishra, M. (2018). Development and optimization of UV-Vis spectroscopy-a review. *World J. Pharm. Res*, *7*(11), 1170-1180.
76. Rina, R., Baile, M., & Jain, A. (2021). A Review: Analytical Method Development and Validation. *Systematic Reviews in Pharmacy*, *12*(11), 3601-3605.
77. Nagy, S., Pál, S., &Széchenyi, A. (2019). Reliability of the Hansen solubility parameters as co-crystal formation prediction tool. *International journal of pharmaceutics*, *558*, 319-327.
78. Gårdebjer, S., Andersson, M., Engström, J., Restorp, P., Persson, M., & Larsson, A. (2016). Using Hansen solubility parameters to predict the dispersion of nano-particles in polymeric films. *Polymer Chemistry*, *7*(9), 1756-1764.
79. Kharisma, R. M., &Sopyan, I. (2017). Dissolution rate repairing of simvastatin as a new approach in cocrystallization. *Der Pharmacia Lettre*, *9*(6), 18-27.
80. Sopyan, I., Fudholi, A., Muchtaridi, M., & Sari, I. P. (2017). Simvastatin-nicotinamide co-crystal: design, preparation and preliminary characterization. *Tropical Journal of Pharmaceutical Research*, *16*(2), 297-303.
81. Ansoborlo, E., Henge-Napoli, M. H., Chazel, V., Gibert, R., &Guilmette, R. A. (1999). Review and critical analysis of available in vitro dissolution tests. *Health Physics*, *77*(6), 638-645.
82. Grignard, E., Taylor, R., McAllister, M., Box, K., &Fotaki, N. (2017). Considerations for the development of in vitro dissolution tests to reduce or replace preclinical oral absorption studies. *European Journal of Pharmaceutical Sciences*, *99*, 193-201.
83. Østergaard, J., Lenke, J., Jensen, S. S., Sun, Y., & Ye, F. (2014). UV imaging for in vitro dissolution and release studies: initial experiences. *Dissolution Technol*, *21*(4), 27-38.
84. Dong, M., & Huynh-Ba, K. (2020). Stability Studies and Testing of Pharmaceuticals-An Overview. *LCGC North America*, *38*(6), 325-336.
85. Narayan, S., & Choudhary, M. (2017). A review on stability studies of pharmaceutical products. *International Journal of Applied Pharmaceutical and Biological Research*, *2*(3), 67-75.

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

87. Kumar, S., & Nanda, A. (2018). Approaches to design of pharmaceutical cocrystals: A review. *Molecular Crystals and Liquid Crystals*, *667*(1), 54-77.

88. Kaur, N., Duggirala, N. K., Thakral, S., &Suryanarayanan, R. (2019). Role of lattice disorder in water-mediated dissociation of pharmaceutical cocrystal systems. *Molecular pharmaceutics*, *16*(7), 3167-3177.

89. González-García, I., Mangas-Sanjuán, V., Merino-Sanjuán, M., & Bermejo, M. (2015). In vitro–in vivo correlations: general concepts, methodologies and regulatory applications. *Drug development and industrial pharmacy*, *41*(12), 1935-1947.

Corresponding email: ***manishkumarsaxena4@gmail.com***