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# CRYSTAL ENGINEERING FOR SOLUBILITY ENHANCEMENT: A REVIEW

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***Abstract :*** Pharmaceutical cocrystals are multicomponent frameworks in which no less than one part is an dynamic drug fixing and the others are chemically acceptable Coformer. Cocrystallization of a medication substance with a coformer is a promising and arising way to deal with work on the presentation of drugs, for example, solubility, dissolution profile, pharmacokinetics and stability. This review article presents a thorough outline of drug cocrystals, choice of coformers and screening of cocrystals have been summed up and various techniques for cocrystal development and assessment have been made sense of. Finally this article features a portion of the synthetic and herbal cocrystals alongside its preparation technique and coformers utilized.

***IndexTerms*** - Cocrystal, Coformer, Solubility, Bioavailability, BCS Class.

## I. INTRODUCTION

As of now, around 90% of new synthetic elements and 40% of at present promoted drugs have a place with the Biopharmaceutical Classification System (BCS) II and IV classes [(1)]. Normal issues that challenge the effective medication conveyance and assembling remember lacks for their properties, like solubility, stability, bioavailability, organoleptic properties and mechanical properties[(2)]. The gastrointestinal plot has different pH in various parts, so medicates when given by oral course have different solubility in gastrointestinal liquids at various pH, frequently prompting nonlinear and variable ingestion and adequacy and wellbeing of medications can't be assessed as expected [(3)]. Cocrystallization is one of the arising gem designing methods for adjusting drug execution through controlling strong state properties of APIs. This is conceivable in light of the fact that cocrystallization altogether grows the admittance to new strong structures varying in structures [(2)].

Cocrystals are solids that are translucent single-stage materials made out of at least two different sub-atomic as well as ionic mixtures by and large in a stoichiometric proportion which are neither solvates nor basic salts [(4)].

A coformer is "a part that interfaces nonionically with the API in the crystal lattice, is definitely not a solvent, and is regularly nonvolatile" [(5)].

Pharmaceutical cocrystals are characterized as crystals that include at least two discrete unbiased particles at a stoichiometric proportion and bond together by means of noncovalent bond connections (e.g., hydrogen holding, van der Waals and pi-pi stacking associations), in which no less than one of the parts is API and the others are chemically adequate coformer [(6)].

## II. ADVANTAGES OF COCRYSTALS

1. Cocrystallization can further develop actual properties like solubility, dissolution, and compressibility, without influencing the pharmacological movement of the API [7].
2. Cocrystallization can be utilized for all dynamic drug fixings including acids, bases, and non-ionizable atoms [8].
3. Another extraordinary benefit of cocrystals over more normal salt structures is that they can be made for non-ionizable APIs [8].
4. As well as medications in complex structures with touchy utilitarian gatherings that may not endure openness to solid corrosive or antacid response conditions [9].
5. Cocrystal likewise exists in a stable translucent structure and doesn't need other excipients or added substances in the definition [10].

## III. LIMITATIONS

1. The planning of co-crystals is straightforward however definite connection between co-crystal structure actual properties still neglected [11].
2. The ideal temperature reach ought to be known for solid-state crushing technique on the grounds that exorbitant warming might cause coincidental stage progress, aggregate crystallization or polymorphism.
3. Solid state crushing technique brings about too little molecule size and henceforth it is challenging to distinguish structure utilizing X-ray crystallography [12].
4. Phase partition of co-crystals into individual part up on capacity at specific relative humidity condition additionally a worry for its materialness [13].

5. Phase change during development of API.
6. Cocrystals may likewise be vulnerable to counter particle removal with excipients during assembling [13].

## IV. SELECTION OF COFORMERS

### 4.1 Hydrogen Bonding Propensity

In cocrystals, API and coformers communicate with one another by non-covalent holding, for example, hydrogen holding and van der Waal forces. Among these, hydrogen holding among API and coformer assumes a significant part in the arrangement of cocrystals[14,15]. Etter has proposed 3 standards for ideal hydrogen bond formation[14,16]:

- each hydrogen particle, which is acidic in nature will be available in bond development,
- all hydrogen bond acceptors will be utilized when there are free hydrogen bond acceptors, and
- hydrogen bond will be shaped when there will be best hydrogen bond donor nand hydrogen bond acceptors.

Hydrogen bond arrangement can be examined by anticipating the contribution of proton givers and acceptors in a gem structure with the assistance of Cambridge structure database[17]. The inclination of hydrogen bond development among contributor and acceptor can be dissected by giving a worth somewhere in the range of 0 and 1. The worth 1 shows the arrangement of hydrogen bond though esteem 0 demonstrates no hydrogen security development.

### 4.2 pKa Approach

Cocrystals or salts arrangement can be anticipated by proton move among corrosive and base. The development of salts or cocrystals can be anticipated by deciding the ΔpKa=[pKa (base)- pKa (acid)]. It is for the most part acknowledged that proton move will happen from corrosive to base assuming the distinction in the pKa values is more noteworthy than 2 or 3. A more modest ΔpKa esteem (under 0) demonstrates the development of cocrystals while higher worth (more than 2 or 3) shows the arrangement of salts[18,19]. ΔpKa rule was approved and measured by examining 6465 cocrystals from CSD and made sense of a direct connection between ΔpKa worth and probability of proton move between corrosive base pair. It was investigated that a non-ionized complex ought to be framed when the worth of ΔpKa<-1; an ionized complex is shaped when the worth of ΔpKa<4 and the chance of development of ionized complex increment by 17% by expansion in ΔpKa by one unit from 10% at ΔpKa=-1 to 95% at ΔpKa=4. By deciding the ΔpKa esteem, the chance of development of cocrystals and salts not entirely settled. This is a basic and less tedious technique for the planning of cocrystals [20].

### 4.3 Supramolecular Synthonic Approach

Desiraju depicted the "synthon approach" for the determination of coformers which shaped a supermolecule by utilizing explicit atomic pieces inside the cocrystal to lay out "supramolecular synthons"[15]. As indicated by this methodology, the practical gatherings present in API and coformer will assume a significant part in the arrangement of cocrystals and coformer with reasonable utilitarian gathering will be utilized for a specific APIs. Synthons are available in the supermolecules as essential underlying units which are related with non-covalent holding. Supramolecular synthon approaches are of two sorts: supramolecular homosynthons and supramolecular heterosynthons. Supramolecular homosynthons are created by same useful gatherings present in API and coformer, for example, the amide homosynthons, carboxylic corrosive homosynthons though supramolecular heterosynthons are framed by various utilitarian gatherings, for example, the carboxylic corrosive amide heterosynthons, the corrosive pyridine heterosynthons[21]. Supramolecular heterosynthons are by and large more preferred than homosynthons, e.g., the corrosive amide and the corrosive pyridine heterosynthons are usually utilized when contrasted with carboxylic corrosive and amide homodimers[22].

### 4.4 Cambridge Structure Database

Cambridge Structure Database (CSD) is significant apparatus to decide the intermolecular associations in crystals. The beginning of the Cambridge Crystallographic Data Center (CCDC) was summed up by Groom and his colleagues in 1965 and improvement of Cambridge Structure Database (CSD) with its significance in the primary science, material sciences and life sciences, including drug disclosure and advancement was summarized [23,24] . CSD is an approved apparatus to work with the measurable examination of pressing themes and subsequently give data about normal useful gatherings. CSD is utilized to give the data about atomic relationship of medication and coformers in light of practical gathering that connect with into supramolecular synthons. A library of reasonable coformers can be ready by CSD for an API. This is a PC based approach used to find proper cocrystal shaping matches, and diminishes the exploration time and exploratory cost[8,22,21].

### 4.5 Hansen Solubility Parameter

Hansen solvency boundary is one more significant methodology used to quantify the miscibility of medication and coformers utilized for cocrystal frameworks. The miscibility of the parts in the strong state could foresee the cocrystal development. The combination of cocrystals achievement rate was improved by utilizing the parts which have comparative miscibility[13]. It was exhibited that the two parts ought to be miscible assuming complete HSPs contrast was <7MPa0.5, in any case immiscible[25]. One more strategy assesses the miscibility of two parts assuming the thing that matters is ≤5 MP0.5 between two substances which should be cocrystal formation[26,27].

### 4.6 COSMO-RS

For evaluating of reasonable coformers for an API, COSMO-therm programming in view of COSMO-RS liquid stage thermodynamic methodology was utilized to portray the miscibility of coformers in super cooled fluid (liquefy) stage. The abundance enthalpy, Hex (a main consideration for H-holding collaborations) among API and coformer combination when contrasted with unadulterated parts mirrors the inclination of those two mixtures to cocrystallize. This was exhibited that COSMO-RS hypothesis permitted sensible positioning of coformers for an API and the tests ought to be centered around those coformers which an expanded likelihood of cocrystallization, prompting the biggest improvement of the API solvency. Along these lines as potential coformers were distinguished for cocrystallization, solvents with most elevated worth of Hex with an API,

were chosen which had minimal likelihood to frame strong solvates. Different coformers for itraconazole and solvents for Axitinib (tyrosine kinase inhibitor) were chosen by this strategy to keep away from development of hydrates and solvents[28].

**4.7 Fabian's strategy:**

Various arrangements of solid cocrystal framing structures were extricated from the CSD and the sub-atomic descriptors (single iota, bond and gathering counts, hydrogen bond benefactor and acceptor counts, size and shape, surface region and sub-atomic electrostatic) were determined for every particle. Based on determined sub-atomic properties, the data set portrayed sets of particles that had the option to shape cocrystals. The most grounded descriptor relationship was connected with the shape and extremity of cocrystal formers[16].

## V. METHOD OF PREPARATION

Various strategies have been accounted for the preparation of cocrystals . Hardly any conventional techniques in view of the solution and grinding were accounted for the preparation of cocrystals[29]. Co-crystals is by and large ready by solvent and solid based methods.

The solvent based methods include -

- Slurry conversion,
- solvent evaporation,
- Solution crystallization technique[30],
- Antisolvent addition [31], and
- Reaction crystallization method[32]

The solid techniques include -

- Neat grinding, and
- Wet grinding

A few recently arising techniques utilized for the arrangement of cocrystals are -

- Ultrasound assisted solution method,[33,34]
- Supercritical fluid atomization technique,[35,36]
- Spray drying technique,[37,38]
- Hot melt extrusion technique[39,40].

**5.1 Slurry Conversion**

It is the interaction where slurry is ready by expansion of various solvents in the combination of API and appropriate coformers. The solvent is drained off and the solid is dried.

**5.2 Solvent Evaporation Method**

The two API and coformer are broken up in an appropriate solvent and the arrangement is permitted to gradually vanish the solvent.

**5.3 Solution Crystallization Technique**

Drug and coformers are broken down in bubbling solvent with blending and the bubbling of the arrangement would be gone on until the volume of the arrangement become little. Cocrystallization happens quickly while the bubbling arrangement is permitted to cool around 15 min. Cocrystals are isolated by filtration and kept in oven or air for drying [30,41].

**5.4 Antisolvent Addition**

The coformers are broken up in various solvents, for example, natural solvents and API is scattered in the coformer arrangement by utilizing scattering homogenizer. This arrangement is then added to refined water or appropriate answer for hasten the coformer on the drug [31,42,43].

**5.5 Reaction Crystallization Method**

The immersed arrangement of the lesser solvent part (drug) is made in methanol and sifted, and afterward the more dissolvable part (coformer) is included a sum simply under its dissolvability limit.

**5.6 Grinding technique**

Grinding procedures are of two sorts: Neat or Dry Grinding and Wet Grinding

**Dry Grinding:** Drug and coformer are combined as one in a stoichiometric proportion and ground them by utilizing either mortar and pestle or ball mill [44] .

**Wet Grinding:** Was acted likewise that of perfect grinding by expansion of certain drops of solvent in the mixture [45,46].

**5.7 Ultrasound assisted solution method**

In this technique, API and cocrystal previous are disintegrated together in a solvent and the arrangement is kept in a sonoreactor to shape the arrangement turbid. Cold water is provided during the sonication to keep up with the steady temperature of sonicator and forestall fracture. The arrangement is kept for the time being for drying.

**5.8 Supercritical fluid atomization technique**

In this method, the drug and coformers are blended in with one another by utilizing high compressed supercritical liquid for example $CO_2$. Cocrystals are ready by atomizing this arrangement with the assistance of atomizer. In supercritical antisolvent (SAS) strategy, the cocrystals are ready from arrangement by the antisolvent impact of supercritical fluid [35,34,47].

**5.9 Spray drying method**

In spray drying process, cocrystals are ready by showering the arrangement or suspension of drug and coformer with hot air stream to vanish the solvent.

**5.10 Hot melt extrusion method**

In hot melt extrusion procedure, the cocrystals are ready by warming the drug and coformers with extraordinary blending which worked on a superficial level contacts without utilization of solvent. The restrictions of this strategy incorporate both coformer and API ought to be miscible in liquid structure and not utilized for thermolabile drugs[48,39,40].

## 6. EVALUATION AND CHARACTERISATION OF COCRYSTALS

The impact of cocrystallization on the properties of the dynamic substance not entirely set in crystal by assessing the subsequent cocrystal solids. Assessment of cocrystal should be possible by solubility study, dissolution study, and stability test. The assessment information can be upheld by portrayal information to guarantee that the subsequent item is a cocrystal and not another strong structure. A few techniques have been applied for the portrayal of drug cocrystals. Portrayal can be done on the construction and actual properties of the cocrystal. The construction of the cocrystal can be broke down utilizing infrared spectroscopy (FTIR) techniques and X-ray diffraction or powder X-ray diffraction (PXRD), while the actual properties are dissected utilizing a melting point estimating instrument like differential scanning calorimetry.

**6.1. Melting point:**

Melting point is one of significant warm way of behaving that could decide the physical stability of medications and lead maker choice in picking suitable assembling course. By and large, the cocrystal melting point would fall between the beginning parts (51%). In any case, it was additionally workable for cocrystal to have lower (39%) or significantly higher (6%) than its beginning components[49].

**6.2. Differential Scanning Calorimetry (DSC):**

To recognize cocrystal development, take a gander at the presence of an exothermic peak followed by an endothermic peak, or change in the melting point of the DSC range. Over half of cases show that the melting point of the cocrystal is lower than the melting point of the particular active ingredient and their coformers [50]. The pure drug, coformer, physical mixture, and cocrystal are put on the aluminum pan and examined with a foreordained warming rate [51].

**6.3. Fourier Transform Infrared Spectroscopy:**

To decide changes in synthetic design and sub-atomic associations that happen in the cocrystal cross section. The cocrystal test was shaped by KBr gem pellets and estimated utilizing an IR spectrophotometer at a wavenumber of 4000-400 cm-1 [52].

**6.4. Nuclear Magnetic Resonance:**

Solid-state NMR (SSNMR) is utilized to portray strong stages that can't be concentrated by SXRD[8]. SSNMR was utilized to explore the idea of complex by deciding level of proton move. In this manner, SSNMR is a significant instrument for the distinguishing proof of cocrystal or salt. SSNMR can likewise be utilized to assess the cocrystal structure by assessing hydrogen holding and nearby conformity changes by couplings[53,54].

**6.5. Powder X-ray diffraction (PXRD):** To figure out the translucent construction of the cocrystal. The examples got from the diffractometer are contrasted and each other. The different XRD designs between the cocrystal and its constituent parts demonstrate the arrangement of the cocrystal [51].

**6.6. Field emission scanning electron microscopy (FESEM):**

FESEM or geography is utilized to concentrate on a superficial level morphology of co-crystals. Micrographs of parts and co-crystals got in the FESEM reads up are used for the examination. In the field emission electron magnifying lens, heat energy isn't utilized purported "cold" source is utilized. A solid electric field is used to discharge the electrons from the outer layer of the conveyor. A tungsten fiber with a slim and sharp needle (tip distance across 10-100 nm) is utilized as a cathode. The field discharge source is connected with a checking electron magnifying lens for the catch of micrographs of co-crystals[33,55-57].

**6.7. Hot Stage Microscopy:**

A mix of microscopy and warm examination is remembered for the hot stage microscopy study. The physicochemical quality of a strong structure is concentrated as a component of temperature and time. The progressions happened while warming the co-precious stone example put on a glass slide are plainly seen under the magnifying instrument for surveying the progressions like dissolving point, liquefying range, and glasslike transformation[58].

**6.8. Dissolution study:**

To know the expansion in the dissolution pace of cocrystal. Used to affirm drug discharge after some time and foresee in vivo execution. Cocrystal tests were tried utilizing a paddle or rotating basket type dissolution apparatus in a reasonable dissolution medium. Then, at that point, the samples is taken in a suitable sum at foreordained time stretches and afterward examined utilizing HPLC or UV instruments [59].

**6.9. Solubility study:**

To decide the solubility of cocrystal contrasted with pure medications or physical mixture thereof. The cocrystal test and the medium are placed into an Erlenmeyer carafe or different compartments, then, at that point, shaken for 24 h at room temperature in the instrument. rotating cup shaker or orbital shaker. After 24 h, the sample is filtered, diluted and estimated with HPLC or UV at the proper wavelength [60].

**6.10. Stability study:**

Comparing the strength and timeframe of realistic usability of cocrystal and pure drug. Commonly utilized temperature and humidity are 40°C/75% RH [61-63] and 25 °C/60% for 1,3 or 6 months[62,64].

**7. APPLICATIONS[65]**

1.The co-crystallization method can be utilized for those medications which are pitifully ionized in nature.
2.Co-crystals can go about as crystallization inhibitor and accordingly super immersion can be kept up with for quite a while during dissolution, which thus assists with accomplishing better bioavailability and controlled arrival of the medication.
3.Bioavailability of API in cocrystal structure can be improved by planning nanosized co-crystals.
4.Co-crystals likewise utilized for the in cycle partition and cleaning of the API.
5.Multi-drug co-crystals (MDC) is likewise acquiring fascination among drug scientists. MDC make synergistic impacts, expanded solvency, bioavailability, and potential to balance out unsound parts through intermolecular cooperations.
6.Nutraceuticals, which are having great medical advantages can likewise be utilized as coformers for better-consolidated medical advantages alongside the API.
7.By utilizing the coformers, for example, saccharin sodium, the unpleasant taste of the API can be adjusted in this manner co-crystallization procedure can be used if there should arise an occurrence of quick dissolving tablets.

**Table 1: List of Cocrystals of BCS Class II Drugs along with their Coformers and Methods of Preparation[66]**

| Sr. No. | Drug | Coformer | Method of preparation |
|---|---|---|---|
| 1 | Telmisartan | Saccharin | Solvent-assisted grinding, Slurry approach and Solution crystallization. |
| | | Glutaric acid | By refluxing a mixture of the two components |
| 2 | Ibuprofen | Nicotinamide | Slow evaporation |
| 3 | Ethenzamide | Gallic acid, 2- nitrobenzoic acid, 3-nitrobenzoic acid, 2,4- dinitrobenzoic acid, 3-toluic acid | Solvent evaporation method |
| | | Glutaric, Malonic, and Maleic acids | Neat grinding and Slow evaporation from solution |
| 4 | Resveratrol | 4-aminobenzamide and Isoniazid | Liquid assisted grinding (LAG) and Rapid solvent removal (RSR) methods |
| 5 | Febuxostat | Urea, Acetamide, Nicotinamide, p-aminobenzoic acid, Saccharin | Liquid-assisted grinding |
| 6 | Mefenamic acid | Nicotinamide | Gas anti-solvent (GAS) process |
| 7 | Felodipine | Glutaric acid | Solvent ultrasonic method |
| | | Xylitol | Wet co-grinding |
| 8 | Nevirapine | Para-Amino Benzoic Acid | Neat grinding |
| 9 | Brexpiprazole | Succinic acid and Catechol | Nano Ball Milling using stainless steel balls |
| 10 | Diacerein | Urea and Tartaric acid | Solvent drop grinding method |
| 11 | Fenofibrate | Nicotinamide | Kneading, Solution crystallization, Antisolvent addition and Solvent drop grinding methods. |
| | | p-Amino Benzoic Acid, Benzoic Acid | Solvent Evaporation Technique |
| 12 | ketoconazole | Nicotinamide 4-Amino benzoic acid | Solvent evaporation method |
| 13 | Nitrofurantoin | Urea , 4-Hydroxybenzoic acid, Nicotinamide, Citric acid, L-Proline and Vanillic acid,Vanillin | Liquid assisted grinding (LAG) methods |
| 14 | Darunavir | Succinic acid | Cooling crystallization method |
| 15 | Piroxicam | Sodium acetate | Dry grinding method |
| 16 | Gliclazide | Succinic acid and Malic acid | Liquid assisted grinding |
| 17 | Tadalafil | Malonic acid Salicylic Acid | Slurry approach , Spray drying, Solvent evaporation method Neat grinding method Co grinding method |
| 18 | Nateglinide | Benzamide | Dry Grinding,Kneading and Solvent |

| | | | |
|---|---|---|---|
| | | | evaporation |
| **19** | Phenazopyridine | Phthalimide | Sonochemical approach |
| **20** | Glibenclamide | Oxalic acid | Solvent Drop Grinding Method |
| **21** | Ezetimibe | L-Proline, Imidazole and Solvate formamide | Wet milling/Grinding or Solution crystallization methods |
| **22** | Naproxen | Picolinamide , Naproxen , Isonicotinamide | Liquid-Assisted Mechanochemistry |
| **23** | Carbamazepine | 2,3-dihydroxy benzoic acid, 1-Naphthoic acid Anthracene-9- carboxylic acid | Liquid assisted grinding |
| **24** | Lamotrigine | Phthalimide, Pyromellitic caffeine, Isophthaldehyde | Solid-state grinding Solvent-drop grinding |
| **25** | Ketoprofen | Malonic acid | Solvent evaporation method |
| **26** | Praziquantel | Citric acid , Malic acid , Salicylic acid and Tartaric acid | Liquid assisted grinding |
| **27** | Tenoxicam | Glycolic acid, 4-Hydroxybenzoic acid, Ketoglutaric acid, Succinic acid , Maleic acid, Malonic acid , Oxalic acid | Solvent-drop grinding |
| **28** | Indomethacin | Saccharin | Cooling batch crystallisation without seeding |
| **29** | Meloxicam | Aspirin | Solution, Slurry, and Solvent drop grinding methods |
| **30** | Griseofulvin | Acesulfame | Solution crystallization technique |
| **31** | Aceclofenac | Sodium Saccharin | Solvent-drop grinding method |
| **32** | Clarithromycin | Urea | Solvent evaporation |
| **33** | Efavirenz | Lactic acid and Adipic acid | Solvent evaporation |
| **34** | Danazol | Vanillin | Solution crystallization |
| **35** | Simvastatin | Aspartame | Slurry approach |
| | | Malic acid | Liquid assisted grinding |
| **36** | Prulifloxacin | Salicylic acid | Solution crystallization method |
| **37** | Lornoxicam | Saccharin, Salicylic acid, Tartaric acid and Pyrogallol | Liquid assisted grinding<br>Reaction co- crystallization<br>Cooling crystallization |
| **38** | Eprosartan mesylate | p- Aminobenzoic, Salicylic acid | Liquid-assisted grinding |

**Table 2: List of Cocrystals of BCS Class III Drugs along with their Coformers and Methods of Preparation[66]**

| Sr. No. | Drug | Coformer | Method of preparation |
|---|---|---|---|
| **1** | Famotidine | Tartaric acid, Maleic acid | Solution method |
| **2** | 5-Fluorouracil | Gentisic acid ,3,4-dihydroxybenzoic acid, 4-aminopyridine | Mechanochemical method |
| **3** | Fexofenadine | Tartaric acid | Solvent evaporation |
| **4** | Apixaban | Oxalic acid | Grinding followed by anti-solvent addition |
| **5** | Pyrazinamide | Malonic acid, Succinic acid, Glutaric acid | Slow evaporation technique |

**Table 3: List of Cocrystals of BCS Class IV Drugs along with their Coformers and Methods of Preparation[66]**

| Sr. No. | Drug | Coformer | Method of preparation |
|---|---|---|---|
| **1** | Aripiprazole | Orcinol ,Catechol, Resorcinol , and Phloroglucinol | Neat grinding (NG), Liquid-assisted grinding (LAG), and Solvent evaporation (SE) |
| **2** | Acetazolamide | Hydroxybenzoic acid and Nicotinamide | Neat grinding (NG) and Reaction crystallization (RC) |
| **3** | Furosemide | Caffeine, Urea, *p*- Aminobenzoic acid, Acetamide, Nicotinamide, Isonicotinamide, Adenine, Cytosine | Liquid-assisted grinding |
| **4** | Etravirine | L-Tartaric acid | Slow evaporation and Physical mixturing |
| **5** | Adefovir dipivoxil | Stearic acid | Antisolvent precipitation |
| **6** | Ciprofloxacin | Nicotinamide | Solvent assisted co-grinding method |

| | | | |
|---|---|---|---|
| **7** | Hydrochlorothiazide | Phenazine, Picolinamide, 4-dimethylaminopyridine | Solution crystallization method |
| | | Piperazine, Isoniazide, Nicotinic acid, Nicotinamide, 4-aminobenzoic acid, Resorcinol, Succinamide | Grinding method |
| **8** | Mesalamine | Glutamine | Liquid assisted grinding |
| **9** | Mefloquine hydrochloride | Benzoic acid, Citric acid, Oxalic acid, Salicylic acid, Pure Mefloquine tablets, Saccharin, Succinic acid | Solution cocrystallization method |
| **10** | Norfloxacin | Isonicotinamide | Slow evaporation technique |
| **11** | Allopurinol | Piperazine, Isonicotinamide, 2,4-Dihydroxybenzoic acid | Solvent evaporation method, grinding method |
| **12** | Ticagrelor | L- tartaric acid, Nicotinamide | Solvent evaporation technique |
| **13** | Docetaxel | Syringic acid | Solvent evaporation method |

**Table 4: List of Herbal Cocrystals along with their Coformers and their Method of preparation[66]**

| Sr. No. | Drug | Coformer | Method of preparation |
|---|---|---|---|
| **1** | Baicalein | Nicotinamide | Slow evaporation, Rotary evaporation,Cogrinding |
| **2** | Betulinic acid | Ascorbic acid | Solubilization of dryg and coformer by using isopropyl alcohol followed by slow evaporation technique |
| **3** | Emodin | Nicotinamide | Slow or Rapid solvent evaporation method |
| **4** | Naringenin | Isonicotinamide , Picolinic acid Betaine | Slurry method , Liquid diffusion method |
| **5** | Hesperetin | Picolinic acid, Nicotinamide and Caffeine | Solvent drop grinding technique |
| **6** | Luteolin | Isoniazid and Caffeine | Liquid assisted grinding method |
| **7** | Curcumin | N-acetylcysteine | Cocrystallization with Supercritical Solvent technique |
| **8** | Caffeine | Hydroxybenzoic Acids | Solution-Mediated Phase Transformation |
| 9 | Quercetin | caffeine:methanol Isonicotinamide Theobromine dihydrate | Slurry method |
| **10** | Genistein | Isonicotinamide | Slow evaporation technique |

## 8. CONCLUSION:

To accomplish the ideal restorative movement of medication, an examination researcher go through a few methodologies that can improve solubility, stability, bioavailability and different boundaries. Cocrystallization is another way to deal with drug industry and co-crystals furnish another bearing to manage issues of ineffectively solvent medications. Co-crystals have more potential than hydrates, solvates and nebulous structures to work on physicochemical properties. Co-crystals exploration will go through co-crystal polymorphism, salt co-crystals, smooth co-crystals and higher request co-crystals in future.

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The author states no conflict of interest.

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