

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

## Cocrystallization in Nutraceuticals

---

Renu Chadha, Yashika Bhalla,  
Maninder Karan Vashisht and Kunal Chadha

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/59365>

---

### 1. Introduction

Food materials that prevent and treat diseases are usually named as functional foods, designer foods, pharma foods and nutraceuticals [1]. Food has been used since ages as a source for the treatment and prevention of various disorders. Enrichment of table salt with iodine and wheat flour with iron/folic acid has been used with an intention to prevent iodine deficiency goiter and anemia for long. Similarly, food fortified with vitamin A has been found to be a feasible and cost-effective approach to reduce vitamin A deficiency [2].

Nutraceuticals very often named as “ *functional foods* ” provides the body with the essential amount of vitamins, fats, proteins and carbohydrates necessary for healthy survival. When functional food assists in the prevention and/or treatment of disease (s) other than deficiency conditions like anemia it is called a “ nutraceutical ” [3].

Nutritional therapy is a healing system using nutraceuticals or phytonutrients for the improvement of human health. It is well known that ancient civilizations used herbal products as a remedy for many diseases. However, specific term for a formulation describing food or its active ingredients, which have medicinal values, was eagerly required. Then, in 1989 term “ Nutraceutical ” was coined by merging the terms “ Nutrition ” and “ Pharmaceutical ” by Dr Stephen DeFelice [4]. “ Nutraceutical ” is a term used for nutritional supplement that is in the market with the objective to treat or prevent disease [5]. Therefore, a “ nutraceutical ” is any matter that may be considered a food or part of a food and provides medical or health benefits. These food products may be categorized as isolated nutrients, dietary supplements and diets to genetically engineered “ designer ” foods, herbal products and processed foods such as cereals, soups and beverages [6]. Dietary supplements play a vital role in premature chronic disease appearance, disease progression, morbidity and mortality. Approximately 40-50% proportion in cardiovascular disorders, 35-50% proportion in cancers, and 20% proportion in

osteoporosis is attributable to dietary factors [7]. These phytonutrients have a big market currently and annual growth rates of nutraceuticals are predicted to increase. This rate expected to be up to 25% for some products [8].

Nutraceuticals include many food and food products, including vitamins, soy products, glucosamine, chondroitin, and many polyphenols and flavonoids (resveratrol, ellagic acid, and quercetin). The vast majority of nutraceuticals are extracted from plant origins; such as fruits, vegetables, roots, and rhizomes. However, many nutraceuticals are derived from animal origins; vitamins and amino acids [9].

However these nutraceuticals suffer from poor solubility and subsequently bioavailability which hinders their formulation as well as utility. The cocrystallization of these nutraceutical is one of the novel strategies to overcome these problems. Cocrystallization of active pharmaceutical ingredients (APIs) with cocrystal formers (or coformers) has gained significant interest in drug-development since the resulting new solid forms are characterized by different physicochemical properties compared to the original API. The presence of many functional groups in APIs, which may form strong supramolecular synthons such as acid...acid, acid...pyridine, acid...amide, amide...amide, amide...pyridine N-oxide, O-H...O, O-H...N, N-H...O and N-H...N offers a great opportunity to design pharmaceutical cocrystals [10-15]. Certainly, cocrystallization increases the diversity of solid-state forms of an API and enhances its pharmaceutical properties such as chemical stability, moisture uptake, mechanical behavior, solubility, dissolution rate and bioavailability. Hence, cocrystallization can directly impact scientific and legal aspects of drug development by providing alternative solid dosage forms and extended patent life.

Significant development on discovery of nutraceutical cocrystals has encouraged numerous studies on cocrystal formation and evaluation. This chapter presents the nutraceuticals cocrystals along with their preparation and characterization and crucial role in enhancing their pharmaceutical parameters.

## 2. Nutraceuticals: Role in therapeutics

Nutraceutical is the combination of “ nutrition ” and “ pharmaceutical ”. In order to modify and maintain normal physiological function nutraceuticals play an important role. The current population and the health trends are the main reasons for the growth and development in the field of nutraceuticals. These nutraceuticals fights against the major health issues of the century such as obesity, cardiovascular diseases, cancer, osteoporosis, arthritis, diabetes, cholesterol etc. In a nutshell, ‘ nutraceutical ’ has lead to the new period of medicine and health, in which the food industry has become a research oriented sector [9].

Consumers being frustrated with the current status of disease-treatment approach with the modern medicines are seeking alternative safer and beneficial products and the bureaucracy of managed care makes nutraceuticals particularly appealing. “ Let food be thy medicine and medicine be thy food ”, quoted by Hippocrates is definitely the precept of today. Nutraceuticals

are the promising class of natural products that demarcates between food and drugs to fade [8]. Even though the use of nutraceuticals by people has a long history, lately scientifically supported nutritional and medical evidence has permitted nutraceuticals to emerge as being potentially effective [16].

Research is now focused on the examination of nutritional food for their protective and disease preventing potential [17]. Nowadays research and development area are exploring different methods for standardization of the nutraceutical compounds or products, carefully develop and execute clinical studies to provide the health claims and benefits to the consumers as well as on the nutraceutical companies. Nutraceuticals have proven to be therapeutically active in the areas starting from common cold, weight problems, sleeping disorders, digestion, blood pressure, cholesterol control, pain killers, depression, anti-arthritic, cardio vascular diseases, diabetes ending up with prevention of certain cancers [18-21].

The nutraceuticals which include Polyunsaturated fatty acid (PUFA), Dietary fibres, Polyphenols, Spices, Prebiotics, Probiotics and Vitamins are the natural food sources (Figure 1) [22,23]. However, these nutraceuticals have high hydrophobicity and are sensitive to external agents such as air, light and oxidative enzymes which constitute a serious problem for their bioavailability. This further hamper their formulation and use. At this point their cocrystal can offer an opportunity to overcome all the issues of nutraceuticals and help in the exponential growth of nutraceuticals market. Cocrystal of nutraceuticals alone or in combination with other preventive and/or therapeutic strategies might become effective future drugs against the most common degenerative diseases. Cocrystals are engineered solids based on the concept of different forms having desired properties using hydrogen bonds, pi-pi stacking and van der waals interactions [9]

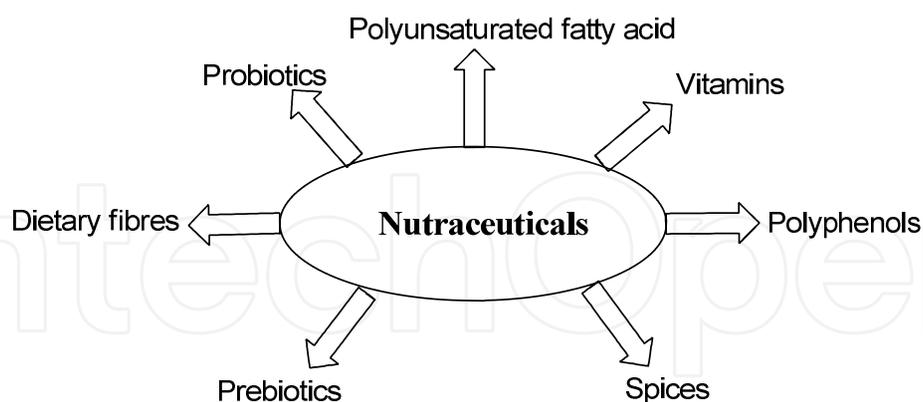


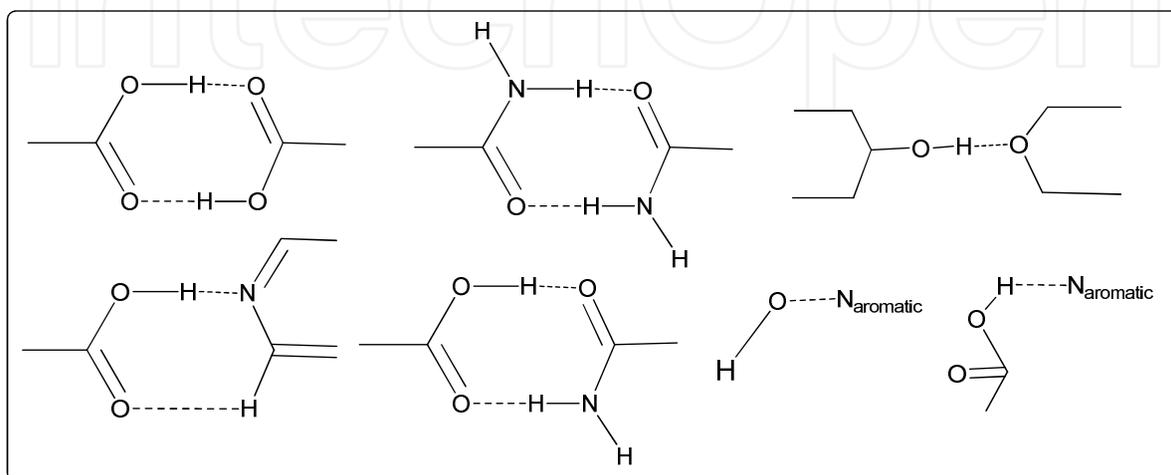
Figure 1. Types of Nutraceuticals

### 3. Cocrystallization

Cocrystals are based on crystal engineering approach which involves the concept of forming new solids (polymorph/solvates and cocrystals/salts) involving non covalent interactions.

Thus nutraceutical cocrystals are multi-component solid-state assemblies formed between a nutraceutical and a cocrystal former of GRAS status bound together in the crystal lattice by any type or combination of non-covalent intermolecular interactions.

Cocrystallization seeks to logically design new form of the nutraceuticals with preferred properties. Depending upon the various potential groups present in these nutraceutical molecules, following heterosynthons are possible (Figure 2) [24] :-



**Figure 2.** Typical Hydrogen Bonds Utilized in Cocrystals

Cocrystallization is at present achieved by a number of techniques including solvent evaporation, dry and wet (solvent drop addition) solid-state grinding, cooling, growth from melts, and slurry conversion. This section covers the various methods of preparation and characterization of the cocrystals.

Different techniques for the preparation of co crystals (Figure 3) [25] are described below:-

1. Solvent evaporation technique :- This is the most commonly used technique in the field of cocrystallization, in this technique stoichiometric amount of the conformer and the drug are dissolved in a common solvent. It is based on the principle that, when different molecules of complementary functional groups afford hydrogen bonds that are more favorable than each of the individual molecular components, the product formed is likely to be thermodynamically favored [26].
2. Solid-state grinding technique :- This technique commonly known as mechanical milling or neat grinding technique. In this method the two cocrystal formers are taken in stoichiometric amounts and ground together using a mortar and pestle, using a ball mill, or using a vibratory mill. Normal grinding time ranges from 30-60 min. It has been reported that cocrystal was first produced by one technique which may be used as seeds to obtain that cocrystal by another method, thus possibly facilitating XRD structure determination via single-crystal growth. In another case, cocrystal structure determination was achieved by preparing only as crystalline powder by grinding [27]

Although co-crystal formation by solid-state grinding has been known for some time and a late 19th century report is often cited as the earliest reference to such a procedure, the recent technique of adding small amounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to increased interest of solid-state grinding as a method for co-crystal preparation [28].

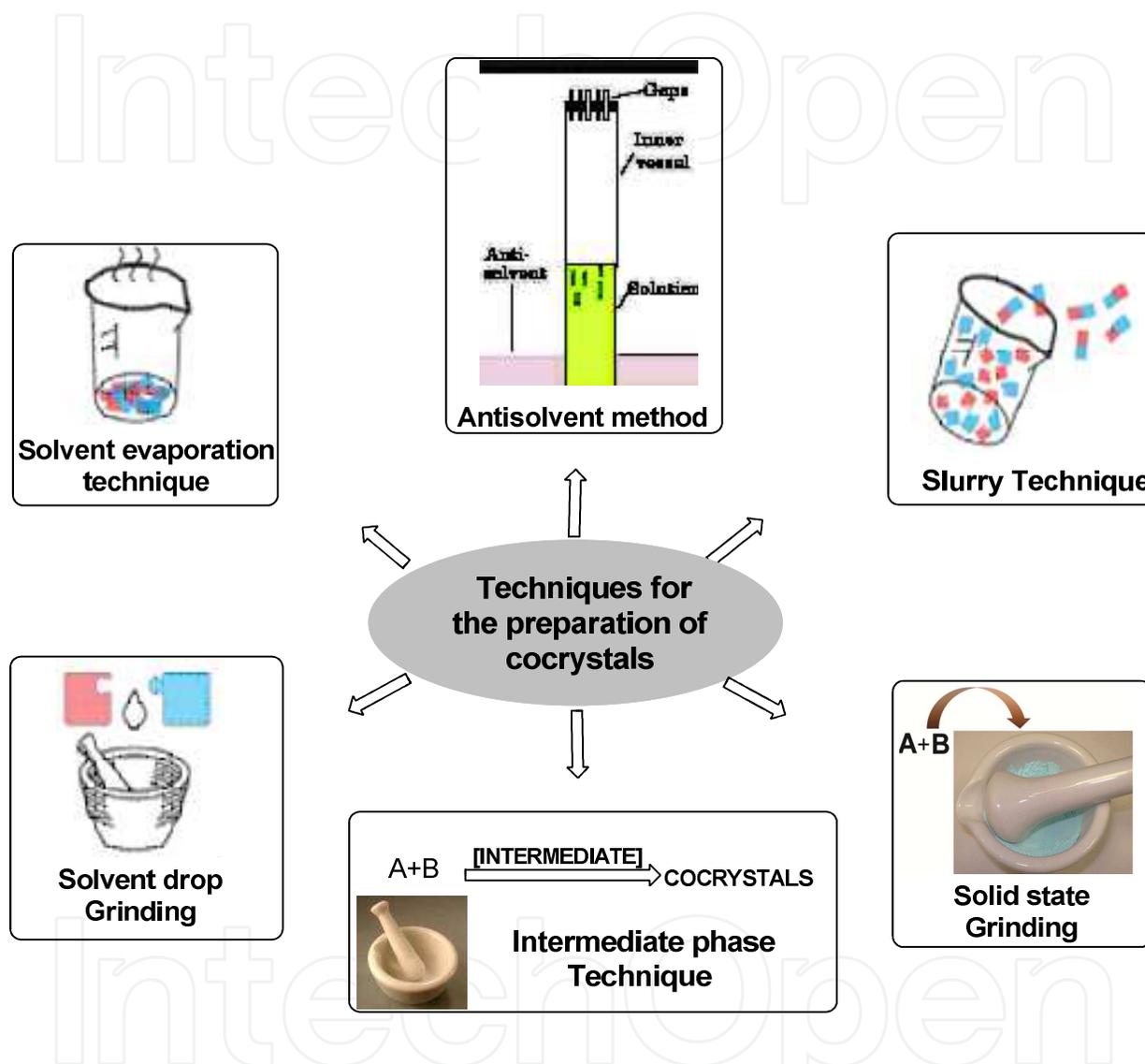


Figure 3. Techniques for the Preparation of Cocrystals

3. Slurring technique:-Slurries-induced formation of cocrystalline phase is among two or more active solid materials or between the active solid materials and the excipients. Equimolar proportion of the two cofomers are dissolved in small amount of different solvents at ambient temperature and allowed to stir for some days. The resulting solution is slowly evaporated at room temperature during 48 hours to promote cocrystallization [29]..Further the solvent is allowed to decant and the solid material is dried under a flow of nitrogen for 5 min. The remaining solids can be characterized using powder X-ray diffraction (PXRD) [30].

4. Solvent drop technique:-This technique also known as liquid assisted grinding or kneading, involving the grinding of stoichiometric amounts of cofomers assisted with a small amount of liquid. This method was developed in order to enhance the rate of cocrystal formation, It also has advantages over solid state grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of cocrystal formers [31].
5. Supercritical fluid technology :-Supercritical fluids is another method by which cocrystals are synthesized.Supercritical fluid technology allows a single-step generation of particles that are difficult or even impossible to obtain by conventional techniques.The unique properties of different super critical fluids assist in generation of pure and dried cocrystals. [32]
6. By using intermediate phase:-Cocrystals can be formed also by using intermediate phases. In the course of time the use of a hydrate or an amorphous phase as an intermediate during synthesis in a solid-state route has proven successful in forming a cocrystal. Besides this, the use of a metastable polymorphic form of one cocrystal former can be used. The metastable form in this technique acts as an unstable intermediate on the nucleation pathway to a cocrystal.
7. Antisolvent addition:-Antisolvent addition also known as vapor diffusion is the methods in which antisolvent is used to synthesize cocrystals.This is one of the methods for precipitation or recrystalization of the two co-crystal former. Solvents consist of buffers (pH) and organic solvents. For example, in the preparation of co-crystals of aceclofenac using chitosan, the chitosan solution was prepared by soaking chitosan in glacial acetic acid. A stoichiometric amount of the drug was suspended in chitosan solution by using high dispersion homogenizer. Further, the dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug [33].

### 3.1. Characterization of cocrystals

This of great importance which can be done using different analytical techniques.Characterization of cocrystals starts from melting point determination and might end up to the technique (Figure 4) employed for the determination of cocrystals.

Thermal analysis:- Differential Scanning Calorimetry (DSC) plays a major role in determining the thermal property testing of cocrystals.DSC is the technique used to observe enthalpy of melting (pharmaceutical cocrystal an overview)during various crystallization events.

Besides this, DSC has recently been used as a screening tool for rapid cocrystal screening [34, 35].It has also been reported that when theophylline and nicotinamide were cogrinded, and from the DSC results it observed that an endothermal peak at about 126.4°C decreased and finally disappeared. A melting endotherm at 171.6°C, which differs from the melting points of either theophylline (271.4°C) or nicotinamide (128.2° C), which indicates that as the cogrinding of theophylline and nicotinamide proceeded, a new phase was formed between theophylline and nicotinamide during the solid- state grinding [36].



Figure 4. Characterization of Cocrystals

Vibrational spectroscopy:-For the characterization of cocrystals molecular motions by use of vibrational spectroscopy are observed. This method includes infrared absorption spectroscopy. Significant changes in the vibrational frequency are observed for the cocrystals and individual constituents confirming the formation of cocrystals. It can be a very useful technique in differentiating cocrystals from salts when a carboxylic acid is involved in hydrogen bonding [37].

It has been reported that in the case of indomethacin and saccharin cocrystals, the O–H stretching of the carboxylic acid group in indomethacin and the N–H stretching of cyclic imide group in saccharin appeared at 3,350.5 and 3,129.1 cm in Indomethacin and saccharin cocrystals, implied the formation of new phase [38].

Crystallographic methods: - Includes single X-ray diffraction (SXR) as well as PXRD. The single X-ray diffraction study offers atomic positions and complete structural information. Powder X-ray diffraction studies using microcrystalline samples become a necessary tool to verify the formation of cocrystal in cases where obtaining single crystal suitable for study becomes bottleneck. SXR is commonly used as supporting information about the formation of a new crystalline phase as in the case of Ciprofloxacin and Norfloxacin cocrystallization [39].

Optical microscopy:-Optical microscopy is the technique used to study crystal morphology. This feature is reflected in the outer appearance of crystals that can be observed by simple hand lens or microscope. To add on, a detailed study can be performed using polarizing optical microscopy, electron microscopy and thermal microscopy. Scanning electron microscopy (SEM), is also used to characterize the surface morphology of the particles. SEM images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. It is applied to determine the cocrystal micrograph and determine the particle morphology in many examples [40-43].

Solid-state nuclear magnetic resonance - These days solid-state NMR is also used for characterization. It studies the chemical environment of the nuclei which is different in cocrystals because of magnetic non-equivalence. In different cocrystals, resonance peaks for the magnetically non-equivalent nuclei will differ. Dipolar correlation experiments between spin pairs such as  $^1\text{H}$ - $^1\text{H}$ ,  $^1\text{H}$ - $^{13}\text{C}$ , and  $^{19}\text{F}$ - $^{13}\text{C}$  are useful to study hydrogen bonding, intermolecular contacts, and spin diffusion to connect individual molecules together in a crystal structure and rapidly establish molecular association [44].

### 3.2. Case studies of some nutraceutical cocrystals

Nutraceuticals such as flavonoids and vitamins have been investigated as candidates for cocrystallization studies to improve their pharmaceutical properties [45].

Flavonoids are natural products and are often studied because of their potent antioxidant and free radical scavenging activities. Nutraceutical cocrystals are associated with higher *in vitro* dissolution rate and *in vivo* bioavailability of their other solid forms, as reported by Smith et al. for quercetin [46] and Epigallocatechin gallate (EGCG). [47].

It has been reported that cocrystallization of flavonoids with 1,4-diazobicyclo [2.2.2]octane (DABCO) resulted in increase in the complexity of these molecules as the number of substituents on the flavonoid backbone increased. Various preparation and properties of flavonoid interactions to the formation of cocrystals with APIs were reported [48].

#### 3.2.1. Protocatechuic acid

Protocatechuic acid (3,4-dihydroxybenzoic acid, Figure 5) is a phenolic acid and belongs to class of polyphenols (Nutraceutical). Protocatechuic acid imparts various pharmacological activity and these effects are due to their antioxidant activities, along with other possible mechanisms, such as anti-inflammatory properties and interaction with several enzymes.

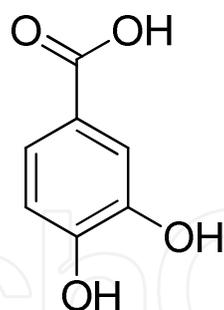


Figure 5. Protocatechuic Acid

S.NO.	Co-former	PA* + Co-Former
1	Caprolactam	 <chem>O=C(O)c1ccc(O)c(O)c1 + O=C1NCCCCC1 &gt;&gt; [MeOH + Water] C7H6O4.C6H11NO</chem>
2	Isonicotinamide	 <chem>O=C(O)c1ccc(O)c(O)c1 + NC(=O)c1cccnc1 &gt;&gt; [MeOH + Water] C7H6O4.C6H6N2O</chem>
3	Isonicotinic Acid	 <chem>O=C(O)c1ccc(O)c(O)c1 + OC(=O)c1cccnc1 &gt;&gt; [MeOH + H2O] C7H6O4.C6H5NO2.H2O</chem>
4	Theophylline	 <chem>O=C(O)c1ccc(O)c(O)c1 + CN1C=NC2=C1C(=O)N(C)C2=O &gt;&gt; [MeOH] C7H6O4.C7H8N4O2</chem>

Table 1. Single crystals of Protocatechuic acid with different coformers [49]

Further in this context, novel 1:1 cocrystals of protocatechuic acid (strong antioxidant) with pharmaceutically accepted molecules (cocrystal formers) such as caprolactam, isonicotinamide, isonicotinic acid, theophylline, nicotinamide and theobromine (Table No. 1) have been obtained by slow evaporation of stoichiometric amounts of starting materials in an appropriate solvent and they were removed from their mother liquors before complete evaporation of the solvent. Cocrystallization via grinding and slurry conversion was also successful to produce 1:1 cocrystals of protocatechuic acid with caprolactam, isonicotinamide, isonicotinic acid, theophylline, nicotinamide and theobromine. The resultant cocrystals were characterized by FTIR, DSC, PXRD, single crystal X-ray diffraction and TGA. [49]

### 3.2.2. Quercetin

Quercetin (3,3',4',5-7-pentahydroxyflavone) (Figure 6), chemically similar to the glycoside rutin, is a unique flavonoid that has been extensively studied by researchers. It has shown to be therapeutically useful in allergic conditions, including asthma and hay fever, eczema, and hives. The frequent link is its ability to mediate production and manufacture of pro-inflammatory compounds. Cocrystal of Quercetin, isonicotinic acid and water (1:1:1) and cocrystal of quercetin, theobromine and water (1:1:2) were obtained (Table no. 2). Quercetin theobromine dihydrate cocrystal resulted in 1.5 fold increase in solubility of quercetin. Quercetin-caffeine-methanol cocrystal was observed after 30 days of slow evaporation of the Quercetin-caffeine-methanol cocrystal solvate. The resulting crystal structure of single crystal of quercetin-caffeine-methanol cocrystal solvate showed that the imide group and the aromatic nitrogen of caffeine interact with the hydroxyl groups of quercetin [50].

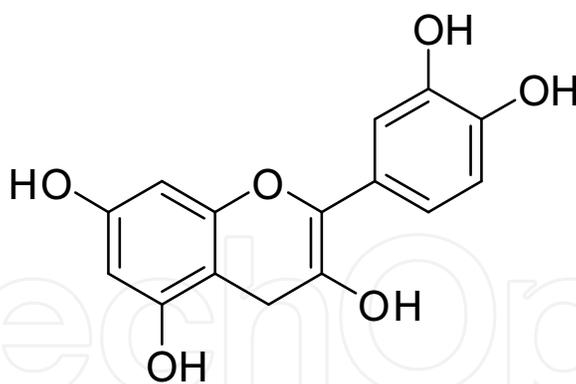
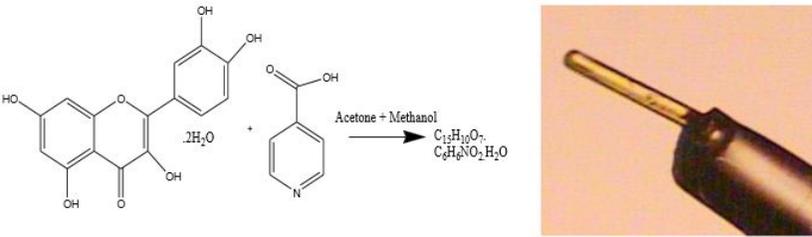
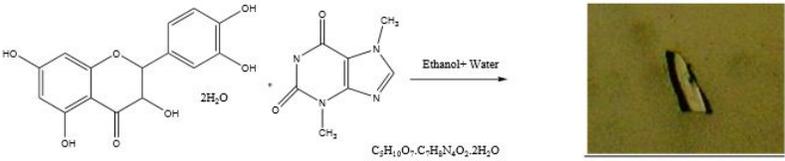


Figure 6. Quercetin

In another attempt for the synthesis of cocrystal of Quercetin with isonicotinamide, quercetin dehydrate and isonicotinamide are dissolved in methanol (5 ml) and heated until a clear solution was obtained. Slow evaporation of this solution in refrigerator resulted in 1:1 crystals after 2 days. Isonicotinamide molecules interact with quercetin molecules via, CO...OH and NH...OH supramolecular heterosynthons and OH...OH supramolecular homosynthons. [50]

Four cocrystals of quercetin (QUE): quercetin: caffeine (QUECAF), quercetin: caffeine: methanol (QUECAF·MeOH), quercetin: Isonicotinamide (QUEINM) and quercetin: theobro-

S.NO.	Co-Former	Quercetin + co-Former
1	Isonicotinic acid + water	
2	Theobromine + water	

**Table 2.** Co-crystals of Quercetin with different cofomers [50]

mine dihydrate (QUETBR·2H<sub>2</sub>O) were prepared by slow evaporation (solution crystallization) method and each of these cocrystals exhibited pharmacokinetic properties that are superior to those of quercetin alone. The QUECAF and QUECAF·MeOH cocrystals increased the solubility of QUE by 14-and 8-fold when compared to QUE dihydrate. Further, the cocrystals outperformed QUE dihydrate with increases in bioavailability up to nearly 10-fold [51].

### 3.2.3. Hesperetin

Hesperetin (Figure 7) which is the aglycone part of hesperedin and is therapeutically very potential molecule as it shows antioxidant, antiallergic, antimutagenic and *in vitro* studies anti cancer activity. Cocrystallization of hesperetin with isonicotinamide resulted in a 1:1 cocrystal. The supramolecular synthon formed in the cocrystal includes OH---N hydrogen bond between the nitrogen atom of isonicotinamide and the OHa of the adjacent hesperetin molecule. Crystallization of hesperetin with nicotinic acid results in two 1:1 cocrystals in which the nicotinic acid exists as a zwitterionic state. Cocrystallization has lead to the generation novel cocrystals of hesperetin with pharmaceutically acceptable molecules such as isonicotinamide and nicotinic acid [52].

### 3.2.4. Pterostilbene

Pterostilbene (Figure 8) is also a nutraceutical which is found in nature in a number of tree barks and a variety of berries, including grapes, as well as plants commonly used in traditional folk medicine. Cocrystals of pterostilbene comprises of cofomers such as: caffeine, carbamazepine. Three cocrystals of a 1:1 stoichiometric molar ratio of pterostilbene with caffeine and carbamazepine were obtained and characterized by crystallographic (XRPD, single-crystal) and thermoanalytical (TGA, DSC) techniques. Physical stability of the reported cocrystals with respect to relative humidity was established to be significantly improved in relationship to

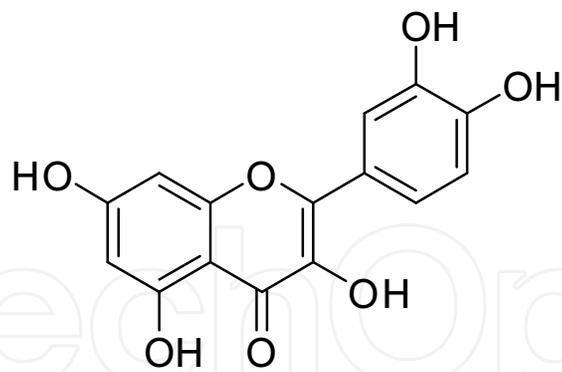


Figure 7. Hesperetin

S.NO.	Co-Former	Single crystal of Hesperetin +conformer
1	Isonicotinamide	
2	Nicotinic acid.	

Table 3. Cocrystals of Hesperetin with different coformers [52]

caffeine or carbamazepine. The carbamazepine: pterostilbene cocrystal was found to be stable upon slurrying in water for 3 days and its solubility was 7× lower than carbamazepine dihydrate and 2.5× lower than pterostilbene [53].

Another study on pterostilbene cocrystallization with pharmaceutically acceptable cofomers piperazine and glutaric acid was reported by Bethune et al. [54]. Cocrystals of a 2:1 and 1:1 stoichiometric molar ratio of pterostilbene with piperazine or glutaric acid were synthesized and evaluated for physical stability with respect to humidity and temperature as well as kinetic solubility. The pterostilbene/piperazine cocrystal disclose a 6-fold increase in pterostilbene concentration compared with the solubility of pterostilbene.

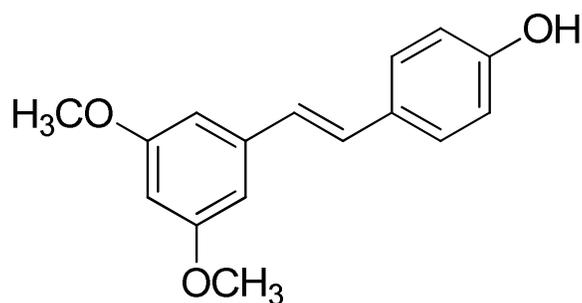


Figure 8. Pterostilbene

### 3.2.5. *p*-Coumaric

*p*-Coumaric (Figure 9) acid is a phytochemical and nutraceutical compound. Cocrystals synthesized with *p*-coumaric acid are explored with xanthine compounds, caffeine and theophylline. Four cocrystals of *p*-Coumaric acid with caffeine (1: 1 and 1: 2 stoichiometric ratios) and was synthesized and their structures determined by single-crystal X-ray crystallography. The two theophylline cocrystals display synthon polymorphism, where both structures possess a carboxylic acid–imidazole heteromeric synthon [55].

In another work reported for polymorphic cocrystals of *p*-Coumaric acid, the nutraceutical was cocrystallized with nicotinamide, producing three polymorphic 1:1 cocrystals and one 2:1 (*p*-Coumaric acid-nicotinamide) cocrystal. Conversion of the 1:1 cocrystals to the 2:1 cocrystal in water was revealed by *in situ* dispersive Raman spectroscopy. An enantiotropic relationship is believed to be existing between two of the 1:1 cocrystals; the third polymorph was likely to be metastable [56].

### 3.2.6. Curcumin

Curcumin, the most important curcuminoid extracted from *Curcuma longa* rhizomes, was commonly used as a spice until its medicinal properties in Indian and Chinese systems of medicine were known and documented. Curcumin (Figure 6) is extensively used as a drug but its utility is hindered due to poor aqueous solubility.

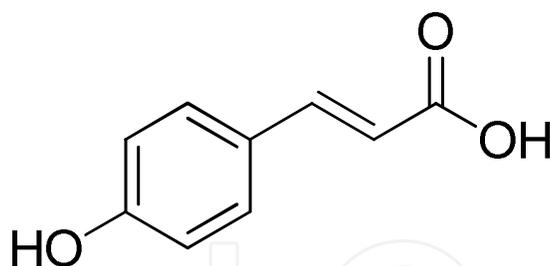


Figure 9. p-Coumaric acid

It has been reported that the cocrystals of curcumin with resorcinol and pyrogallol were obtained by solvent drop method. Cocrystals of Curcumin–resorcinol and curcumin–pyrogallol were obtained in stoichiometric ratio of 1: 1 and were characterized by X-ray diffraction, thermal analysis, FT-IR, FT-Raman, and solid-state  $^{13}\text{C}$  NMR spectroscopy. The melting point of the cocrystals was found to be between that of curcumin and the conformer, it has been observed that the lower melting cocrystal was more soluble than higher melting. The dissolution studies revealed that the dissolution rates of curcumin–resorcinol and curcumin–pyrogallol in 40% EtOH–water are ~5 and ~12 times faster than that for curcumin [57].

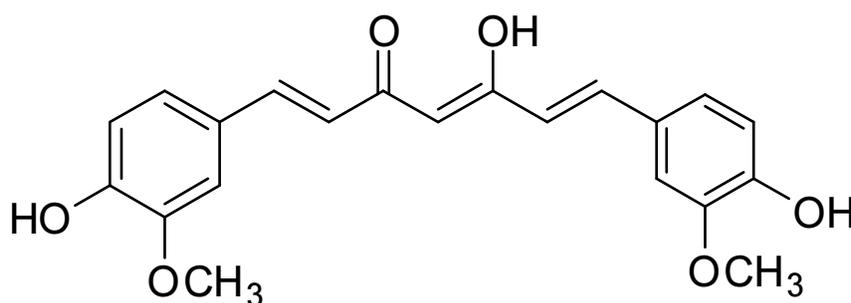


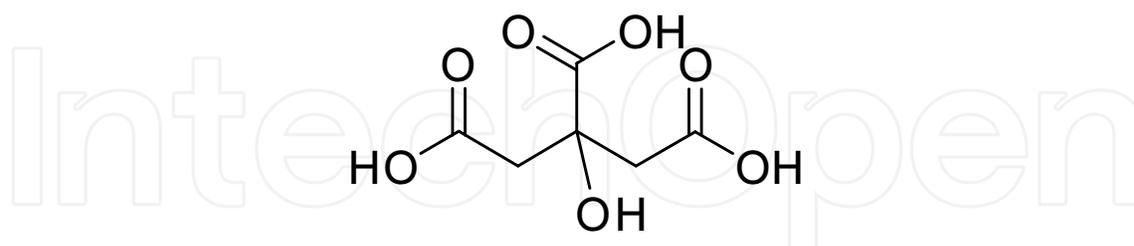
Figure 10. Curcumin

### 3.2.7. Citric acid

Citric acid (2-hydroxy-1, 2, 3-propanetricarboxylic acid) is a weak tricarboxylic acid that is naturally concentrated in citrus fruits. Citric acid is commonly used as a food additive to provide acidity and sour taste to foods and beverages. Citrate salts of various metals are used to deliver minerals in biologically-available forms; examples include dietary supplements and medications. Citric acid is known as a highly soluble and safe nutraceutical. Since citric acid is highly soluble it may be used as conformer in the field of cocrystallization.

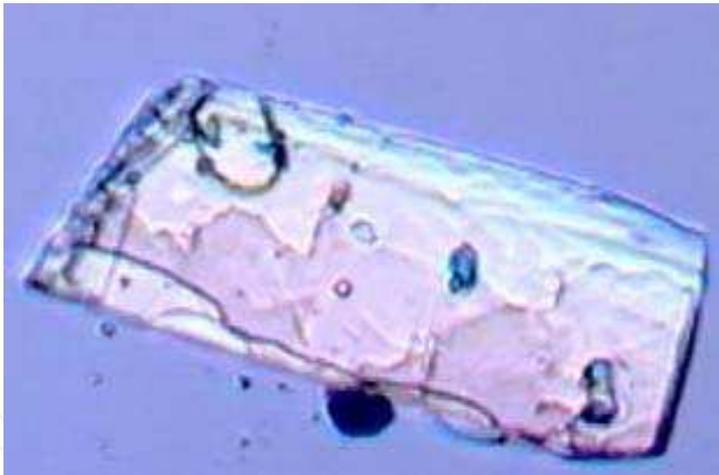
It was reported that Citric acid (Figure 11) and paracetamol in 2:1 stoichiometric ratio formed cocrystals. Notable changes were observed in the IR spectra of the cocrystal. IR spectra of cocrystal were different from that of the raw materials by several vibrational frequencies. The asymmetric unit of the crystal has two paracetamol molecules hydrogen-bonded to the citric acid; one of these behaves as a phenolic-OH hydrogen bond donor to the carbonyl of a

carboxylic acid arm of citric acid. In contrast, the other phenolic-OH acts as a hydrogen bond acceptor from the quaternary C–OH of citric acid [58].



**Figure 11.** Citric acid

Dalia et al., had reported about the formation of a novel cocrystals of citric acid resulting in the formation of single crystals (Table no. 4). Cocrystal of citric acid in 2:1 ratio with isonicotinamide was reported and X-ray crystal structure indicates that molecules of *iso*-nicotinamide form hydrogen bonds with molecules of citric acid [59].

S.NO.	Co-Former	Single crystal
1.	Isonicotinamide	

**Table 4.** Cocrystal of Citric acid

### 3.2.8. Gossypol

Gossypol (Figure 12) is a natural product occurring as biphenolic compound derived from the cotton plant (genus *Gossypium*). Wang et al. in 2009 reported the (-)-gossypol cocrystals with a C1–8 carboxylic acid or C1–8 sulfonic acid which are inhibitors of anti-apoptotic Bcl-2 family proteins. The invention also relates to inducing apoptosis in cells and for sensitizing cells to the induction of apoptotic cell death by the cocrystals of (-)-gossypol with a C1–8 carboxylic acid or C1–8 sulfonic acid [60].

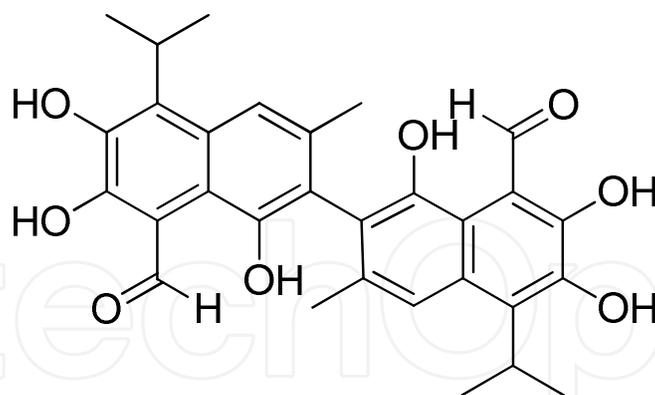


Figure 12. Gossypol

### 3.2.9. Fisetin, Luteolin, Genistein

Fisetin, Luteolin and Genistein (Figure 13) are natural polyphenolic compounds belonging to nutraceuticals. Crystallization studies were carried on these molecules with nicotinamide and isonicotinamide as coformers. Five cocrystals were isolated, characterized by X-ray single-crystal diffraction, FT-Raman spectroscopy, thermal analysis (DSC and TG-DTA),  $^1\text{H}$  NMR in solution and compared in terms of supramolecular motifs. Fisetin–nicotinamide (1: 2) ethanol hemisolvate (**FisNam**), fisetin–isonicotinamide (1:1) (**FisInam**), two polymorphic forms of luteolin–isonicotinamide (1: 1) (**LutInam**, **LutInam2**) and genistein–nicotinamide (1:1) monohydrate (**GenNam**) cocrystals reveal the presence of an  $\text{OH}\cdots\text{N}$  (atom) heterosynthon between an O7 hydroxyl moiety of a flavonoid and the pyridyl ring of a conformer [61].

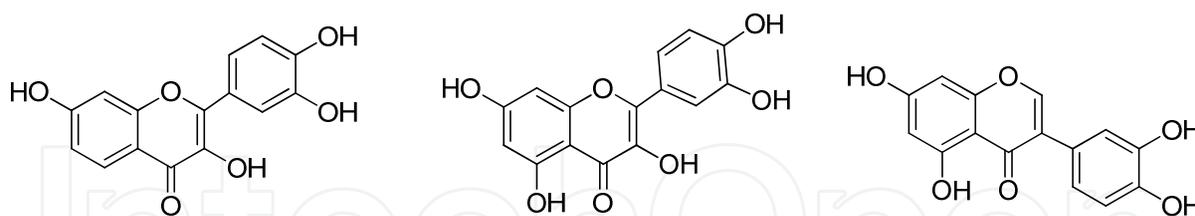


Figure 13. Fisetin, Luteolin and Genistein

Genistein (Figure 13) is a phytoestrogen and belongs to the category of isoflavones. Genistein and Caffeine formed 1:1 cocrystalline phase, which was formed by means of a solvent-drop grinding experiment and isolated later in a solution-evaporation approach. Resulting cocrystal was characterized by X-ray single-crystal and powder diffraction and the cocrystals were explored in terms of thermal stability and Hirshfeld surfaces. A scale-up procedure by slurry method, facilitated solubility studies. Neutral forms of both compounds cocrystallize in a common P21/c space group of the monoclinic crystal system. Crystal lattice discloses formation of molecular layers, formed by  $\text{O}-\text{H}\cdots\text{O}$ ,  $\text{O}-\text{H}\cdots\text{N}$  and  $\text{C}-\text{H}\cdots\text{O}$ -type contacts between genistein and caffeine molecules, while stabilization of the three-dimensional crystal lattice is

offered by pi - pi interactions. Dissolution studies showed maximum solubility of the cocrystalline phase in a 50:50 v/v ethanol–water medium, attained 0.861 mg/mL after 8 h, revealing some degree of enhancement as compared to parent genistein, maximum solubility of which was also reached after 8 h and equaled to 0.588 mg/mL [62].

#### 4. Conclusion

These natural products are of interest because of their proposed health-promoting effects as antioxidants and anticarcinogens. In spite of the immense biological activities revealed by nutraceuticals still these phytochemicals cannot be exploited due to their biopharmaceutical issues which hinder their utility. However, their high hydrophobicity and sensitivity to external agents such as air, light and oxidative enzymes constitute a serious problem for their bioavailability and formulation. However, bioavailability and solubility troubles coupled with these natural entities can be improved by formulating them into cocrystals. The cocrystallization strategy may optimize some potential nutraceuticals. Cocrystal of nutraceuticals alone or in combination with other preventive and/or therapeutic strategies might become effective future drugs against the most common degenerative diseases. Though studies on cocrystallization of nutraceutical molecules are going on, still there is a lot to be explored so as to utilize these potential molecules for severe disease.

#### Author details

Renu Chadha\*, Yashika Bhalla, Maninder Karan Vashisht and Kunal Chadha

\*Address all correspondence to: renukchadha@rediffmail.com

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

#### References

- [1] Kwak NS, Jukes DJ. Functional foods. Part 1: the development of a regulatory concept. *Food Control*. 2001;12 (2)99-107
- [2] Bele AA, Khale A. An approach to a nutraceutical. *Research Journal of Pharmacy and Technology*. 2013; 6 (10)1161-1164
- [3] Kalra EK. Nutraceutical-definition and introduction. *American Association of Pharmaceutical Scientists*. 2003; 5 (3) 27-28.
- [4] Brower V. Nutraceuticals: poised for a healthy slice of the healthcare market? *Nature biotechnology*. 1998;16 728-732.

- [5] Zeisel SH. Regulation of " nutraceuticals". *Science* 1999;285:1853-1855.
- [6] Eskin M, Tamir S. *Dictionary of nutraceuticals and functional foods*: CRC Press; 2004.
- [7] Gupta S, Yadav SK, Patil S. Nutraceutical: a bright scope and oppourtunity of Indian healthcare market. *International Journal of Research and Development in Pharmacy and Life Sciences* 2013; 2 (4) 478-481.
- [8] Adelaja AO, Schilling BJ. Nutraceuticals: blurring the line between food and drugs in the twenty-first century. *Choices*. 1999;14 (4).
- [9] Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of nutraceuticals in human health. *Journal of food science and technology*. 2012;49 (2) 173-183.
- [10] Reddy LS, Babu NJ, Nangia A. Carboxamide–pyridine N-oxide heterosynthon for crystal engineering and pharmaceutical cocrystals. *Chemical Communications*. 2006 (13) 1369-1371.
- [11] Bhogala BR, Basavoju S, Nangia A. Three-component carboxylic acid-bipyridine lattice inclusion host. *Supramolecular synthesis of ternary cocrystals*. *Crystal Growth & Design*. 2005;5 (5) 1683-1686.
- [12] Reddy LS, Basavoju S, Vangala VR, Nangia A. Hydrogen bonding in crystal structures of N, N'-Bis (3-pyridyl) urea. Why is the NH tape synthon absent in diaryl ureas with electron-withdrawing groups? *Crystal Growth & Design*. 2006;6 (1) 161-173.
- [13] Shattock TR, Vishweshwar P, Wang Z, Zaworotko MJ. 18-Fold interpenetration and concomitant polymorphism in the 2: 3 Co-crystal of trimesic acid and 1, 2-bis (4-pyridyl) ethane. *Crystal Growth & Design*. 2005; 5 (6) 2046-2049.
- [14] Bhogala BR, Nangia A. Cocrystals of 1, 3, 5-Cyclohexanetricarboxylic Acid with 4, 4'-bipyridine homologues: acid pyridine hydrogen bonding in neutral and ionic complexes. *Crystal Growth & Design*. 2003;3 (4) 547-554
- [15] Aakeröy CB, Hussain I, Desper J. 2-Acetaminopyridine: A highly effective cocrystallizing agent. *Crystal Growth & Design*. 2006;6 (2) 474-80.
- [16] Dillard CJ, German JB. Phytochemicals: nutraceuticals and human health. *Journal of the Science of Food and Agriculture*. 2000;80 (12) 1744-1756
- [17] Nicoli M, Anese M, Parpinel M. Influence of processing on the antioxidant properties of fruit and vegetables. *Trends in Food Science & Technology*. 1999;10 (3) 94-100.
- [18] Pandey M, Verma RK, Saraf SA. Nutraceuticals: new era of medicine and health. *Asian Journal Pharmaceutical Clinical Research*. 2010;3 (1) 11-15.
- [19] Sami Labs—pioneer in nutraceuticals August 05, 2002. *The Hindu Newspaper* :<http://www.hinduonnet.com/thehindu/biz/2002/08/05/stories/2002080500040200.htm>

- [20] Espín JC, García-Conesa MT, Tomás-Barberán FA. Nutraceuticals: facts and fiction. *Phytochemistry*. 2007;68 (22) 2986-3008.
- [21] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997;275 (5297) 218-220.
- [22] Kalia AN. Textbook of Industrial Pharmacognocny, CBS publisher and distributor, New Delhi, 2005, pp. 204–208
- [23] Kokate CK, Purohit AP, Gokhale SB. Nutraceutical and Cosmaceutical. *Pharmacognosy*, 21st edition, Pune, India: Nirali Prakashan, 2002 pp. 542–549
- [24] Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: an overview. *International Journal of Pharmaceutics*. 2011;419 (1):1-11.
- [25] Review on cocrystal as an approach with newer implications in pharmaceutical field
- [26] Jayasankar A, Somwangthanoj A, Shao ZJ, Rodríguez-Hornedo N. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. *Pharmaceutical Research*. 2006;23 (10) 2381-2392.
- [27] Zaini E, Sumirtapura YC, Soewandhi SN, Halim A, Uekusa H, Fujii K. Cocrystalline phase transformation of binary mixture of trimethoprim and sulfamethoxazole by slurry technique. *Asian Journal of Pharmaceutical and Clinical Research*. 2010;3 (4).
- [28] Blagden N, De Matas M, Gavan P, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*. 2007;59 (7):617-630.
- [29] Tiekink ERT, Vittal JJ (Editors). *Frontiers in Crystal Engineering*, John Wiley & Sons, Ltd, Chapter 2: Crystal Engineering of Pharmaceutical Co-crystals, 2006, pp. 25-50
- [30] Yadav A, Shete A, Dabke A, Kulkarni P, Sakhare S. Co-crystals: a novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian Journal of Pharmaceutical Sciences*. 2009;71 (4):359.
- [31] Jung J, Perrat M. Particle design using supercritical fluid: literature and patent survey. *Journal of Supercritical Fluids*. 2001;20 179-219.
- [32] Basavoju S, Boström D, Velaga SP. Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. *Pharmaceutical Research*. 2008;25 (3) 530-541.
- [33] Mutalik S, Anju P, Manoj K, Usha AN. Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach. *International Journal of Pharmaceutics*. 2008;350 (1) 279-290.
- [34] Lu E, Rodríguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. *Crystal Engineering Communication*. 2008;10 (6) 665-668.

- [35] Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. *International Journal of Pharmaceutics*. 2011;407 (1) 63-71.
- [36] Lu J, Rohani S. Preparation and characterization of theophylline–nicotinamide cocrystal. *Organic Process Research & Development*. 2009;13 (6) 1269-1275.
- [37] Aakeröy CB, Fasulo ME, Desper J. Cocrystal or salt: does it really matter? *Molecular Pharmaceutics*. 2007;4 (3):317-22.
- [38] Basavoju S, Boström D, Velaga SP. Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. *Pharmaceutical Research*. 2008;25 (3) 530-541.
- [39] Pinto Vitorino G, Sperandeo NR, Caira MR, Mazzieri MR. A supramolecular assembly formed by heteroassociation of ciprofloxacin and norfloxacin in the solid state: co-crystal synthesis and characterization. *Crystal Growth & Design*. 2013;13 (3) 1050-1058.
- [40] Velaga SP, Basavoju S, Boström D. Norfloxacin saccharinate–saccharin dihydrate cocrystal–A new pharmaceutical cocrystal with an organic counter ion. *Journal of Molecular Structure*. 2008;889 (1) 150-153.
- [41] Johnson S, Rumon K. Infrared spectra of solid 1: 1 pyridine-benzoic acid complexes; the nature of the hydrogen bond as a function of the acid-base levels in the complex1. *The Journal of Physical Chemistry*. 1965;69 (1) 74-86.
- [42] Jung MS, Kim JS, Kim MS, Alhalaweh A, Cho W, Hwang SJ, et al. Bioavailability of indomethacin-saccharin cocrystals. *Journal of Pharmacy and Pharmacology*. 2010;62 (11) 1560-1568.
- [43] Padrela L, Rodrigues MA, Velaga SP, Matos HA, de Azevedo EG. Formation of indomethacin–saccharin cocrystals using supercritical fluid technology. *European Journal of Pharmaceutical Sciences*. 2009;38 (1) 9-17.
- [44] Vogt FG, Clawson JS, Strohmeier M, Edwards AJ, Pham TN, Watson SA. Solid-state NMR analysis of organic cocrystals and complexes. *Crystal Growth and Design*. 2008;9 (2) 921-937
- [45] Chadha, R.; Saini, A.; Arora, P.; Bhandari, S. Pharmaceutical cocrystals: a novel approach for oral bioavailability enhancement of drugs. *Critical Reviews™ in Therapeutic Drug Carrier Systems*. 2012, 29, 183–218.
- [46] Smith AJ, Kavuru P, Wojtas L, Zaworotko MJ, Shytle RD. Cocrystals of quercetin with improved solubility and oral bioavailability. *Molecular Pharmaceutics*. 2011;8 (5):1867–1876.

- [47] Smith AJ, Kavuru P, Arora KK, Kesani S, Tan J, Zaworotko MJ, et al. Crystal engineering of green tea epigallocatechin-3-gallate (EGCg) cocrystals and pharmacokinetic modulation in rats. *Molecular Pharmaceutics*. 2013;10 (8):2948-2961.
- [48] Timmons DJ, Bernas AA, Pacheco MR, Fricke KA. Crystal engineering with flavonoids; The 235th ACS National Meeting, New Orleans, LA, April 6–10, 2008; <http://oasys2.confex.com/acs/235nm/techprogram/P1163554.HTM>
- [49] Pujari TA. Cocrystals of nutraceuticals: Protocatechuic acid and quercetin, 2009. Theses and Dissertations. Paper 2156; <http://scholarcommons.usf.edu/etd/2156>
- [50] Kavuru P. Crystal engineering of flavonoids, Master of Science, Department of Chemistry, College of Arts and Sciences, University of South Florida; <http://purl.fcla.edu/usf/dc/et/SFE0002463> <http://scholarcommons.usf.edu/etd/325/>
- [51] Smith AJ, Kavuru P, Wojtas L, Zaworotko MJ, Shytle RD. Cocrystals of quercetin with improved solubility and oral bioavailability. *Molecular Pharmaceutics*. 2011;8 (5):1867–1876.
- [52] Jin GZ, Yamagata Y, Tomita K. Structure of naringin hexahemihydrate. *Acta Crystallographica*. 1990;C46:310–313
- [53] Schultheiss NC, Bethune SJ. Pterostilbene cocrystals. United States Patent Application 20110189277, 08/04/2011; <http://www.freepatentsonline.com/y2011/0189277.html>, Schultheiss N, Bethune S, Henck JO. Nutraceutical cocrystals: utilizing pterostilbene as a cocrystal former. *Crystal Engineering Communication* 2010;12:2436–2442.
- [54] Schultheiss N, Bethune S, Henck JO. Nutraceutical cocrystals: utilizing pterostilbene as a cocrystal former. *Crystal Engineering Communication*. 2010;12 2436–2442.
- [55] Bethune SJ, Schultheiss N, Henck JO. Improving the poor aqueous solubility of nutraceutical compound pterostilbene through cocrystal formation. *Crystal Growth & Design*. 2011;11 (7) 2817–2823.
- [56] Schultheiss N, Roe M, Boerrigter Stephan XM. Cocrystals of nutraceutical *p*-coumaric acid with caffeine and theophylline: polymorphism and solid-state stability explored in detail using their crystal graphs. *Crystal Engineering Communication* 2011, 13 (2) 611-619.
- [57] Melanie J. Bevill \*, Petinka I. Vlahova, and Jared P. Smit. Polymorphic Cocrystals of Nutraceutical Compound *p*-Coumaric Acid with Nicotinamide: Characterization, Relative Solid-State Stability, and Conversion to Alternate Stoichiometries.
- [58] Sanphui P, Goud NR, Khandavilli UBR, Nangia A. Fast dissolving curcumin cocrystals. *Crystal Growth & Design*. 2011;11 (9) 4135–4145.

- [59] Elbagerma MA, Edwards HGM, Munshi T, Scowen IJ. Identification of a new cocrystal of citric acid and paracetamol of pharmaceutical relevance. *Crystal Engineering Communication*. 2011;13 1877–1884.
- [60] Aboarayas DA. *Crystal engineering of nutraceutical cocrystals*: University of South Florida; 1820.
- [61] Wang S, Chen J. Gossypol co-crystals and the use there of. 03/26/2009, Patent application number:20090082445.
- [62] Sowa M, Ślepokura K, Matczak-Jon E. Cocrystals of fisetin, luteolin and genistein with pyridinecarboxamide cofomers: crystal structures, analysis of intermolecular interactions, spectral and thermal characterization. *Crystal Engineering Communication*. 2013;15 (38):7696-708.
- [63] Sowa M, Ślepokura K, Matczak-Jon E. Solid-state characterization and solubility of a genistein-caffeine cocrystal. *Journal of Molecular Structure*. 2014; 1076: 80–88