REVIEW PAPER

Drug-Nutraceuticals Cocrystals: Advancing Biopharmaceutical and Therapeutic Performance

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ABSTRACT

A drug molecule's physicochemical attributes like its bulk characteristics, solubility, dissolution, mechanical properties and stability are critical determinant of their bioavailability and therapeutic performance, yet often pose serious challenges during formulation development. Cocrystallization offers a unique approach to address these challenges by forming crystalline complexes of an Active Pharmaceutical Ingredient (API) with a suitable conformer, typically a Generally Recognized as Safe (GRAS) compound, in a defined stoichiometric ratio. Unlike salt forms, cocrystals are stabilized by interactions that are non-covalent in nature, like van der Waals forces, hydrogen bonds and π-π stacking, enabling modulation of key drug properties including solubility, permeability, dissolution, compressibility and stability. Nutraceuticals have emerged as promising conformers, offering dual benefit of altering physicochemical properties of API while also providing antioxidant and anti-inflammatory effects. This review highlights recent advances in the design, synthesis and characterization of drug-nutraceutical cocrystals. Exploring the ongoing formulation development and approved market products, the review highlights the potential of drug-nutraceutical cocrystals in advancing personalized medicine.

Keywords: *Cocrystals, Nutraceuticals, Bioavailability, Solubility, Cocrystallization*

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INTRODUCTION

Drugs or active pharmaceutical ingredients (APIs) occur in several different solid states like crystals, amorphous, anhydrous, hydrates, salts, cocrystals, etc. Every form exhibits distinct physicochemical characteristics that have the potential to significantly impact the drug's bioavailability, purity, stability and other performance attributes. The compound's thermodynamically most stable crystalline form is typically the most preferred solid form. However, especially for water-insoluble chemicals, the stable crystal form may show poor oral absorption owing to insufficient solubility or dissolution rate. In order for drug compounds to be bioavailable in the body, they must be soluble in aqueous medium[1,2,3,4].

Almost 80% of existing medications are orally administered as solids, which is a widely accepted safe dosage form and is thought to be most convenient. However, low solubility affects about 40% of them; in fact, low solubility issues affect between 80 to 90% of potential drug molecules in the research and development (R&D) stage. Salt formation, prodrug formation, solid dispersions, size reduction, inclusion complexes with cyclodextrins, self-emulsifying formulations, surfactants, polymorphs, nanoparticles, and multi-component molecular crystals are some of the most commonly employed methods to increase the solubility of APIs. Cocrystallization approach stands apart from the remaining techniques by the fact it effectively improves the drug's bioavailability and a number of physicochemical characteristics without changing its pharmacological characteristics[5,6,7,8].

It is well-established that the characteristics of a particular crystalline substance are directly influenced by the crystal lattice's atomic arrangement. Therefore, by adjusting the crystal packing configurations, it is possible to change the physicochemical characteristics of solid drug forms. Through alteration of the underlying crystal structure, cocrystallization with an appropriate coformer presents the possibility of improvised solubility, thus making the drug readily bio-available. The solubility, stability, and bioavailability of such APIs are all enhanced through these tailored solid forms. By strategically combining a drug with a suitable coformer—often a small organic molecule, such as a sugar or an amino acid—researchers can manipulate the crystal lattice to create a new phase with desirable characteristics. There is ample evidence of improvements in solubility, stability, bioavailability, and mechanical qualities, and emerging applications like flavour masking and patent extension are being studied[1,4,6,9].

2. FUNDAMENTALS OF COCRYSTALLIZATION

Pharmaceutical Cocrystals as defined by US-FDA are “crystalline material composed of two or more different molecules typically an API and cocrystal former (coformer) in the same crystal lattice." According to EMA "solid that is crystalline single phase material composed of two or more different molecular and or ionic compounds, generally in a

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stoichiometric ratio, which is neither solvates nor simple salts." So, essentially Cocrystals are crystalline materials that contain two or more different molecular components that are bonded by interactions of non-covalent nature. Co-crystals are held together via numerous non-covalent interactions like π stacking, hydrogen bonding and Vander-Waals forces. US-FDA recognizes cocrystals as just another polymorph of the parent API and categorizes it under DPI (Drug Product Intermediate). On the other hand the EMA treats cocrystals as another salt of the same API keeps it under regulatory status of API[1,5].

2.1. Advatages of co-crystallization- Essentially, only APIs containing ionisable groups are capable of forming salt, whereas practically The ability of all molecules, weakly ionisable and non-ionizable APIs included, to form cocrystals offers a superior method for improving the physical characteristics of such APIs. Owing to toxicological restrictions, only molecules with acidic or basic counter-ions have been studied for salt formation, thus limiting the choice of counter-ions. However, for cocrystallization, several different potential cocrystal conformers are available that are free from toxicological limitations. It's also critical to keep in mind that salt formation typically targets a single basic and acidic functional group. Co-crystals, on the other hand, are able to target several functional groups in a single therapeutic molecule at once[1,6].

US-FDA defines coformer as "a component that interacts non-ionically with the API in the crystal lattice, that is not a solvent (including water), and is typically nonvolatile". Coformers and medications can modify a cocrystal system's pharmaceutical characteristics. Therefore, it is essential to take into account the physicochemical characteristics of coformers while forming a cocrystal. When considering poorly water-soluble APIs for cocrystallization, the physicochemical characteristics of the conformers, like their ionization and solubility, must be taken into account. The US FDA maintains a list of substances “generally recognized as safe” GRAS list, which enlists thousands of commonly used and possible co-formers for pharmaceutical cocrystals, is a list of compounds that are generally accepted to be safe. Another class of materials with an established history of safety that can be used as viable cocrystallization candidates in the pharmaceutical industry is natural nutraceuticals[1,10,11].

Fig. 1: Advantages of Cocrystallization & its impact on pharmaceutical attributes of API.

Because of the various co-crystal-forming functional groups on their backbone, nutraceuticals with related health benefits or even therapeutic qualities function well as co-formers. They make an excellent choice for coformers because of their organic origins, well-known pharmacological profile, along with their ready availability, in addition to providing a dual therapeutic approach. Simultaneously, their addition can produce synergistic therapeutic benefits along with improving the drug's physicochemical characteristics. Nutraceuticals are incorporated into the cocrystals in order to improve the APIs' poor physicochemical characteristics—such as stability, solubility, and bioavailability. Additionally, APIs that are vulnerable to oxidation can be stabilised by utilising the antioxidant qualities of nutraceuticals. Furthermore, cocrystallization with GRAS-acceptable conformers can improve the performance of nutraceuticals with well-established health advantages but subpar physicochemical characteristics[11,12,13].

2.2. Selection of coformers- Interactions between coformer's functional groups and that of the API are followed by interactions between additional functional groups. Such frequently found functional groups involved in cocrystallization are carboxylic acids, amides, and alcohols. When utilising a specific coformer to make cocrystals, aspects including the nature of functional group, pKa values, their molecular weight along with physical form must be taken into account. The knowledge-based approach and experimental methods are the main methods used while selecting the coformer. Several factors like Hydrogen-bonding tendency, Hansen solubility parameter, pKa-based models, supramolecular synthon compatibility using the Cambridge Structure Database (CSD), computation of lattice energy, thermal analysis, saturation temperature measurements, virtual cocrystal screening (using molecular electrostatic potential surfaces, or MEPS), etc. are taken into consideration for the selection of suitable coformers[6,10,14].

3. TYPES OF COCRYSTALS:

The number of elements in the crystal lattice determines whether the cocrystals are classified as binary, tertiary, or quaternary. Also depending upon the nature of conformer they can be either molecular cocrystals or ionic cocrystals[5].

3.1. Binary cocrystals

They consist of a single crystal lattice with two components, i.e. API and coformer, in a certain stoichiometric ratio. The pharmacological properties of the drug do not change because the conformer only affects the novel solid form's physiochemical properties. Binary cocrystals are more likely to succeed since they only involve two distinct components that are interacting. Some examples of such binary cocrystal formulations are Naproxen-Nicotinamide (2:1), Caffeine-oxalic acid (2:1), Indomethacine-saccharine (GRAS sweetener) (1:1), Malonic acid-famotidine, Fluoxetine hydrochloride-succinic acid (2:1), cocrystals[15,16,17].

3.2. Tertiary cocrystals

Ternary cocrystal's crystal structure has three neutral solid-state components, joined together by hydrogen and/or halogen bonding in a specific stoichiometric ratio. When binary cocrystals are unable to change the physicochemical parameters, ternary cocrystals offer an effective replacement. It is substantially more challenging to combine three components into a stoichiometric ternary cocrystal form, wherein all components are all solids under normal conditions. To create a ternary cocrystal, intermolecular interactions and crystallisation must be well balanced. To create a stable ternary cocrystal, a delicate balance of interactions and solubilities must be attained. As a result, so far there have been comparatively limited observations of ternary or higher cocrystals. However, a study published in 2015 utilized supramolecular synthons of the carboxylic acid and sulfonamide functional groups to produce five distinct ternary cocrystals of p-sulfonamide benzoic acid (SMBA) with pyridine amides and lactam coformers[18,19].

3.3. Ionic cocrystals (ICC)

Depending on the existence of metal cations, ICCs can be defined multi-component crystal lattices where the constituents are associated by coordination or hydrogen bonding. The main constituents of ICC are acid salts and conjugate acid-base cocrystals. A variety of solid-state properties can be altered by cocrystallizing a drug molecule (organic) with a coformer that is inorganic in nature. However, the drug's salt form is more thermodynamically stable than the ionic cocrystals. In 2010, the Braga group was the first to write about ICC, emphasising on the barbituric acid's solubility characteristics and how these characteristics changed when ICC was synthesised using caesium iodide and alkali bromides. Zinc trifluoro-methanesulfonate is used to form an ionic cocrystal of 6-mercaptopurine, which significantly increases the compound's water solubility[15,20,21].

3.4. Molecular cocrystals (MCC)

A stoichiometric ratio of at least two neutral molecular compounds (coformers) bound together by non-covalent interactions like halogen or hydrogen bonding characterizes these crystalline solids. Earlier these MCCs were referred as "hydrogen bond complexes", "molecular organic compounds" and "organic molecular compounds", etc[5,22,23,24].

3.5. Nano-cocrystals (NCC)

Certain limitations, like precipitation of API due to the dissociation of conformer in cocrystals & physical stabilization during milling in case of nanocrystal formulation, render these individual techniques insufficient for pharmaceutical development. Therefore, the benefits of co-crystallization are combined with nano-crystallization in order to obtain novel nano-cocrystal formulations. Despite being a relatively new prospect, some research on such formulations are reported, such as nano-cocrystals of Indomethacin-Saccharin, Carbamazepine-Saccharin, Myricetin-nicotinamide, Itraconazole-Adipic acid, Furosemide-Caffeine, Baicalein-Nicotinamide, etc. with promising improvement in their respective physico-chemical properties[25,26,27].

4. METHODS FOR DESIGNING COCRYSTALS

4.1. Synthon engineering- In organic synthetic chemistry, Corey in 1967 first used the term "synthon". It was described as "structural units within a molecule which are related to possible synthetic operations." This technique is based on the idea that cocrystal formation is encouraged by molecular similarity. Heterosynthons and homosynthons are examples of supramolecular synthons. Two like complementary functional groups (such as dimers of amide-amide & carboxylic acid-acid) create crystalline complexes in supramolecular homosynthons, while two differing complementary functional groups produce crystal complexes in heterosynthons. Acidamide, hydroxylamine, hydroxylpyridine, and acidpyridine are a few examples of such heterosynthons[2,28,29].

The formation of heterodimer should be favoured rather than a homodimer by the driving force in order for cocrystal formation to take place. Utilizing the energy differences, the most appropriate interaction between two molecules can be predicted. For instance, the Cambridge Structure Database (CSD) data indicates that about 48.5% of crystal structures contain the acid-pyridine hetero-synthon, while merely 4.1% exhibit the acid homo-synthon. Consequently, it is reasonable to assume that, in comparable circumstances, an acid-acid bond holds advantage over an acid-pyridine bond. The possibility of creating new molecular entities is greatly enhanced by the capacity to statistically anticipate the heterosynthon formation among two molecules. Because of hydrogen bonding, the OH—O synthon is the strongest, followed by the NH—O synthon. The synthon method was used to identify the olanzapine-hydroquinone cocrystal[29,30].

4.2. Crystal Structure Prediction- The cocrystal's intermolecular energy contribution is termed as its lattice energy. In simpler words the energy needed to break apart a crystal lattice is the lattice energy. Using DFT (Density Functional Theory), the difference in intramolecular energy can be determined by the transformation in molecular conformation from the gaseous phase. These computations can be optimised via Crystal Structure Prediction (CSP),

which predicts the thermodynamic stability and structure of cocrystals, enabling a comparison of the energy of different packing configurations. The structure of crystal and the motifs present in the cocrystal structure can be determined with the aid of CSP. It is less likely for an API and a coformer to associate if their lattice energies are high. Theoretically, they are also less likely to come together if the atoms in the API crystal lattice have higher force of attraction than compared to the conformer's atom [5,31,32].

4.3. Cambridge Structure Database Established in 1965, CSD is a frequently updated database of small-molecule organic and metal-organic crystal structures, following thorough expert validation and verification. The Coformer's shape and polarity serve as the primary foundation for the CSD. Each entry in the CSD provides details about stereochemistry, conformational analysis, crystal packing, molecular dimensions, molecular geometry, chemical structure, and crystallographic data including space groups, crystal systems, lattice and symmetry. It consists of crystallographic data about the hydrogen bonding developed between the API and the coformer. More than 1.2 million crystal structures are currently available in the CSD library[10,33,34].

It is an extremely useful tool for retrieving, displaying, and analysing experimentally obtained crystallographic data, which enables better comprehension of the behaviour of molecules and the interactions among molecules in crystals better. For the desired cocrystal structure, supramolecular synthetic analysis can be performed using the database. Coformers are chosen for cocrystallization with the APIs based on the geometries and preferred orientations of the existing intermolecular interactions[6,35,36].

4.4. Hydrogen Bonding Propensity- Since hydrogen bonding promotes the production of cocrystals, an empirical study of hydrogen bonding patterns can prove useful when constructing cocrystals following specific standards. The hydrogen bonds are preferentially established by the best hydrogen-bond donor and the best hydrogen-bond receiver. Nearly all suitable proton donors (like -COOH, -NH4+) and acceptors (like -OH, -NH3) are used in hydrogen bonding. In contrast to inter-molecular hydrogen bonds (like N-H---O and O-H---O), intra-molecular hydrogen bonds with a six-membered ring (like C-H---O) are formed first. Once the intra-molecular hydrogen bond formation is completed, the best remaining proton donors and acceptors then participate in inter-molecular hydrogen bonding. By ranking the target system's H-bonding propensities, the HBP model aims to ascertain the likelihood of each potential H-bond formation. In order to generate a statistical model, the HBP tool uses the 2D properties of a collection of structures that contain functional groups and molecules that are comparable to the API molecule[36, 37].

4.5. Hansen solubility parameter- The cocrystals, at the molecular level, are miscible systems. Additionally, predicting the probability of cocrystal formation can be done by determining the miscibility of the constituent molecules in the solid state. According to the idea of solubility parameters, which were first proposed by Hildebrand and Scott, materials would be miscible if their solubility parameters were equal. Because the crystal lattice energy and salvation energy (polarity) influences the solubility, the concept that "like dissolves like" came into existence. The concept behind the solubility parameter (δ) is that the total energy of various interactions can be broken down into partial solubility parameters, such as hydrogen bonding (δh), polarity (δp), and dispersion (δd). Using the HSP program, the space coordinates of the Hansen Space are composed of these three HSP parameters. A solution is more likely to develop when two molecules dissolve in one another because their solubilities are more similar and their interaction radius is less the closer they are to one other in this space. This technique was used in cocrystal screening to anticipate the API's miscibility with a coformer; cocrystal formation is likely if the solubility parameter for a given API is less than a specific value (e.g. 7 $MPa^{½}$ for carbamazepine)[5,6,28].

4.6. pKa rule- A common approach for predicting the formation of salt is the pKa rule. For acid-base cocrystals, it may assist in lowering the count of possible coformers under consideration. The equilibrium reaction constant for acid dissociation is Ka. A coformer's capacity to form cocrystals with a particular API has been analysed using the difference in pKa (ΔpKa) value. According to the rule, an acid-base complex is presumed to form a cocrystal or a solvate if the ΔpKa values between a conformer and API (or another API in the case of drug-drug cocrystals) fall between 0 and 3. Salt formation is expected to happen if the pka value is greater than three. The formation of a cocrystal will occur below a pka value of 0[37,38].

4.7. Fabian's method- By examining the chemical descriptors of the molecules in a cocrystal, Fabian developed the molecular complementarity tool. The CSD was used to extract a wide range of credible cocrystal-forming structures. Each molecule's molecular descriptors—such as its size, shape, surface area, electrostatics, number of hydrogen bond donors and acceptors, number of bonds and groups, and single atoms—were then estimated. The database listed molecular pairs that might form cocrystals based upon estimated molecular properties. It was discovered that the polarity and molecular shape of the molecules that form cocrystals are typically identical. APIs lacking common functional groups for effective hydrogen bonding benefit greatly from the Molecular Complementarity tool[37,39].

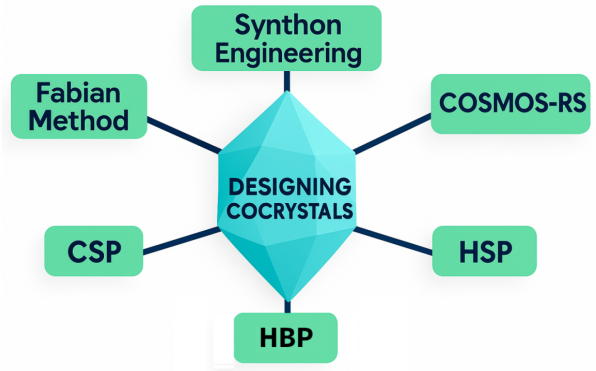

Fig. 2: Various tools available for designing cocrystals.

4.8. COSMO-RS- Andreas Klamt proposed Conductor-like Screening Model for Real Solvents concept, which is an innovative fusion of liquid phase thermodynamics along with the quantum chemistry that is employed to project thermodynamic equilibrium features of liquids with high accuracy. A COSMO-RS fluid-phase thermodynamic technique based COSMO-therm program, is used to investigate the coformer's miscibility in their molten (super-cooled liquid) phase in order to screen appropriate coformers for an API. Consequently, by evaluating the affinities between the super-cooled conformer and the API cocrystallization can be predicted. The excess enthalpy (Hex) of the mixture of conformer and API in comparison to the enthalpy of individual pure cocrystal formers indicates the possibility of cocrystallization of the components. The cocrystal system is more likely to be thermodynamically favourable if Hex has a larger negative value[34,40].

4.9. Hammett constants- Hammett constants can be used to help screen for an effective formation of acid-acid cocrystals. The Hammett constant determines a functional group's tendency to donate electron and electron-withdrawing properties, in relation to the standard benzoic acid functional group. Since significant variations in the electron-removing impact of two components are equivalent to significant variations in pKa values, this method and the pKa method are closely related. It is discovered that combining components with opposite-sign Hammett constants suggests a very likely cocrystal formation. A favourable interaction is indicated by an increase in dimer binding energies, which explains the growing difference in Hammett constants. The difference in the dimer's total energy and the sum of the energies of the two separate monomers is known as the dimer binding energy. Further salt creation is more likely than cocrystal formation as this difference grows[28, 41,42].

4.10. Machine learning- Utilising a variety of algorithms, this rapidly evolving discipline has been used to construct cocrystals. ANNs (Artificial Neural Networks) have been utilised to cluster data into groups according to comparable metrics, for screening coformers. This method makes advantage of the molecular structures of two coformers and, using data taken from the data set, generates the likelihood of co-crystal formation. It is feasible to train ANNs for predicting cocrystal formation by utilizing the existing data on binary cocrystals from CSD with a sizable collection and combining it with combinations of unfeasable coformers. Its link with the Cambridge structural database means that when additional crystal structures are added to the database, predictions will become more accurate. The method's excellent efficiency (accuracy ≥97%) was validated in silico, and accuracy values of about 80% are expected in situations when one of the molecules is not present from co-crystals in the CSD[28,43].

5. METHODS OF PREPARATION

5.1. Solid state methods

This method includes mixing the API and coformer together in molten state, leading to the formation of the cocrystals. As the research points that the rate of cocrystallization for premilled reactants is faster, in certain situations, a quick grinding of the pure components is carried out separately before mixing. Likewise, it has been noted that cocrystallization rates are higher in systems with higher relative humidity and temperatures. Three separate steps are typically involved in the moisture uptake process that leads to cocrystallization: (1) Uptake of moisture, (2) Dissolution of the components, and (3) Nucleation of cocrystals and its growth. Typically, it involves sonication, melt extrusion, and solid phase grinding (applied to both wet and dry solid mixes) at temperatures between 80 and 85°C. Contact formation, solid state grinding, high shear wet granulation, liquid-assisted grinding, twin screw extrusion (TSE), hot melt extrusion (HME), and other processes are employed under this technology[4,6].

5.2. Solution based methods

Supersaturation is a key factor in crystallisation. The concentrations of the coformer and the drug molecule are two crucial variables to take into account in a cocrystal system. The supersaturation for cocrystallization is determined by both the API and conformer's concentrations, in relation to the cocrystal's solubility, which is best described in reference to the drug molecule and coformer. A ternary phase diagram (TPD) provides the most realistic representation of a cocrystal system's solubility. Additionally, it has been proposed that there is a structural flexibility in such molecular compounds exhibiting polymorphism and that there is a larger likelihood of bringing the component into a new packing arrangement while coexisting with another component. The method employs techniques like Isothermal slurry conversion, Cooling crystallization, Evaporative crystallization, Reaction cocrystallization, Anti-solvent method, Spray drying, Ultrasound aided cocrystallization, Spray flash evaporation process, Super-critical fluid atomization, etc[4,5,6,20].

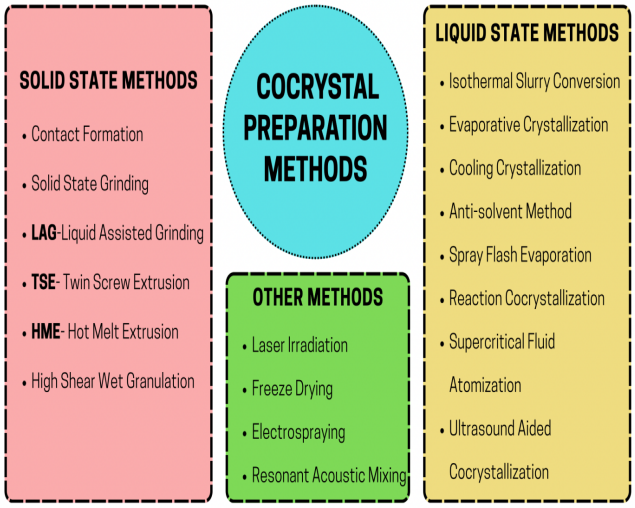

Fig. 3: Various methods used for formulating cocrystals.

5.3. Miscellaneous methods

More recently, techniques like Electrospray technology, Laser irradiation, Freeze drying, Electrochemically induced cocrystallization, Resonant acoustic mixing, etc. are also reportedly being explored for cocrystal production[5,20].

6. CHARACTERIZATION TECHNIQUES FOR SCREENING OF COCRYSTALS

Recent advancements in PXRD (powder X-ray diffraction) and SCXRD (single-crystal X-ray diffraction) continue to provide definitive evidence of cocrystal formation by revealing unique diffraction patterns that distinguish new multi-component phases from parent APIs and coformers. PXRD remains the cornerstone screening technique due to its rapidity, reliability, and clear lattice fingerprinting. When single crystals are available, SCXRD delivers comprehensive structural details—including molecular arrangement and hydrogen bonding motifs—confirming supramolecular synthons within the cocrystal lattice. FTIR (infrared spectroscopy) serves as a complementary tool, observing characteristic shifts in vibrational bands, especially N–H or C=O stretching, to infer new interactions formed upon coformer integration[2,44,45,46].

Emerging vibrational spectroscopic methods such as THz-TDS (terahertz time-domain spectroscopy), low-frequency Raman, and THz-Raman have significantly enhanced sensitivity in cocrystal screening by probing lattice vibrations and phonon modes indicative of the cocrystal rather than mere physical mixtures. Recent studies demonstrate that THz-Raman can distinguish not only cocrystal formation but also polymorphic transitions in solid-state reactions, offering real-time monitoring capability in mechano-chemical processes. These techniques are increasingly integrated with chemo-metric analysis, enabling automated classification and high-throughput screening during development. For instance applying **PCA** (Principal Component Analysis) on Raman spectral data can help in differentiating between pure API, Coformer, physical mixture and cocrystals. Similarly, Partial lease Square Regression, **PLSR** can be used to monitor the extent of cocrystal formation by correlating spectral changes with XRD or DSC[47,48].

7. RECENT ADVANCES AND RESEARCH TRENDS

Nutraceutical research is constantly expanding, not only because of their possible health advantages but also owing to their apparent medicinal benefits in a variety of medical conditions, including relief in cold, pain, cough, digestive problems, sleep disorders, etc. and minimising the risk of some types of cancer. Despite having many advantageous qualities (such as antioxidants, anti-inflammatory, analgesics, etc.), being easily patented, and being widely accessible over-the-counter, nutraceuticals have not yet been widely used as coformers in cocrystallization. A small number of research have investigated the cocrystallization of APIs with nutraceuticals, primarily flavanoids and phenolic acids, with little focus on vitamins. The improvement of these cocrystals' solubility, dissolution, permeability, and physical stability has received more attention. Cocsystal formation has also proven successful in changing the solubilities and bioavailability of certain nutraceuticals, such as flavonoids, stilbenes and phenolic acids[10,11,13].

Table 1: List of pharmaceutical Drug-Nutraceutical cocrystals studied with enhanced properties.

Nutraceutical (coformer)	API	Properties Enhanced	References
Aspartic acid	Itraconazole	3x Solubility	49
Ascorbic acid	Curcumin	576x Solubility	50
Betaine	Epalrestat	2x Solubility, Photostability	51
Cinnamic acid	5-Fluorouracil	Permeability	52
	Lamotrigine	Flow properties	53
Gallic acid	Milrinone	Solubility, Permeability	54
Glycine	Itraconazole	2.3x Solubility	51
Nicotinic acid	Glibenclamide	3x Solubility	55
L-Asparagine	Rosuvastatin	2.1x Solubility	56
L-Proline	Diclofenac	7.5x Solubility	57
Tartaric acid	Acyclovir	5x Solubility	58
	Glimepiride	4x Dissolution	59
Succinamide	Hydroclhlorthiazide	2.4x Solubility	60
Serine	Itraconazole	2.5x Solubility	51
Syringic acid	Milrinone	Solubility, Permeability	54
4-Hydroxy-benzoic acid	Nitrofurantoin	Physicochemical & Photo-stability	61
4-Hydroxy-benzoic acid	5-Fluorouracil	Permeability	52
Ferrulic acid	Favipiravir	5.5x Solubility	62
Nicotinamide	Ceritinib	119x Solubility	63

	Baicalein	6x Solubility	25
	Entacapone	Solubility, Permeability	64
	Metaxalone	8.6x Solubility	65
	Tranilast	Photostability	66
Fumaric acid	Acyclovir	5.5x Solubility, stability	58
	Axitinib	11.7x Solubility	67
	Berberine	9.5x Solubility	68
	Diltiazem	16.5x Solubility	69
	Enoxacin	9.8x Solubility	70
	Efavirenz	26x Solubility	71
	Glipizide	2.3x Solubility	72
	Sidenafil	5x Solubility	73
Oxalic acid	Telmisartan	11.7x Solubility	74
	Rebamipide	7x Solubility	75
	Glibenclamide	2.7x Solubility	76
Succinic acid	Eprosartan mesylate	61x Solubility	77
	Fluoxetine HCl	3x Dissolution	78
	Glibenclamide	2.5x Solubility	55
	Loratadine	2x Solubility	79
	Piperine	12..7x Solubility	80
	Temozolomide	Chemical stability	81
Citric acid	Metformin HCl	1-4x Solubility	82
	Rebamipide	12.5x Solubility	75
	Pyrazinamide	1.4x Dissolution	83
	Simvastatin	1.5-3x Dissolution	84
	Praziquantel	2-4 x Solubility	85
	Glimepiride	2.5x Dissolution	59

8. REGULATORY AND COMMERCIAL PERSPECTIVE

Pharmaceutical cocrystals are recognized by major regulatory agencies, with some key distinctions. The U.S. FDA (2018) classifies cocrystals as solid-state forms of APIs, akin to polymorphs rather than salts, allowing their inclusion in NDAs and ANDAs without being treated as separate intermediates. Notably, cocrystals can be listed in the Orange Book under drug substance patents, enhancing opportunities for intellectual property protection. In contrast, the European Medicines Agency (EMA, 2015) takes a more conservative approach, treating cocrystals similarly to salts and requiring comprehensive characterization, coformer justification, and adherence to Directive 2001/83/EC. If new cocrystals can demonstrate bioequivalence they qualify for generic applications in the EU. This regulatory divergence impacts development strategies, particularly in terms of dossier preparation, bioequivalence requirements and patent filing[86,87].

Table 2: Key differences between pharmaceutical cocrystals, salt and polymhic form of a drug

Aspect	Cocrystals	Salts	Polymorphs
Definition	API + neutral coformer; no ionization.	API + counter-ion; forms ionic compound.	Different crystalline form of API
Bonding	Non-covalent (e.g., hydrogen bonds).	Ionic bonding (electrostatic attraction).	Intermolecular forces
pKa Requirement	Not required.	ΔpKa > 2–3 needed for salt formation.	Not applicable
Solubility	Improves solubility/dissolution without ionization.	Improves solubility via ionization/dissociation.	Variable
Permeability	May increase lipophilicity and permeability.	Often decreases lipophilicity; may lower permeability.	Variable
Stability	More stable across pH and humidity variations.	Can be less stable; prone to hygroscopicity	Variable
Examples	Nicotinamide, citric acid, caffeine, etc.	Sodium, hydrochloride, sulfate, etc.	Carbamazepine, Paracetamol, etc.

8.1 Commercial Cocrystal Preparations

Depakote® is an cocrystal approved by FDA that has an A+B−B drug substance. Pharmaceutical ICCs are also possible, in which two distinct drug molecules act as coformers. Entresto®, a hydrated A+B−B′-co-crystal, consists of sodium salts of sacubitril and valsartan. Seglentis®, an A+B−C co-crystal, in which A for protonated tramadol, an analgesic, and B for chloride & C stands for celecoxib, an anti-inflammatory agent[24,88,89].

Table 3: List of US-FDA approved commercially available cocrystal products

Product name	API	Coformer	Property altered
Lexapro	Escitalopram	Oxalate	Stability
Depakote	Valproic acid	Valproate sodium	Hygroscopicity, Stability
Suglat	Ipragliflozin	L-Prolin	Stability, Hygroscopicity
Beta chlor	Chloral hydrate	Betaine	Stability
Entresto	Valsartan	Sacubitril	Permeability
Steglatro	Ertugliflozin	Z-Pyroglutamic acid	Permeability, Stability
Seglentis	Celecoxib	Tramadol HCl	Solubility
Cafcit	Caffeine	Citric acid	Dissolution, Hygroscopicity
Abilify	Aripiprazole	Fumaric acid	Solubility, Thermal stability
Mayzent	Siponimod	Fumaric acid	Solubility, Stability
Odomzo	Sonidegib monophosphate	Phosphoric acid	Solubility, Stability
ESIX-10	Escitalopram oxalate	Oxalic acid	Solubility
Zafatek	Trelagliptin	Succinic acid	Solubilty, Stability

9. ROLE IN PERSONALIZED MEDICINE

One of the core challenges in personalized medicine is designing drug formulations that are precisely adapted to an individual's pharmacokinetic and pharmacodynamic profile. Cocrystallization offers a solution by modifying key drug properties, like solubility, dissolution rate and bioavailability, without significant alteration in the drug molecule. When nutraceuticals such as flavonoids (like quercetin), polyphenols (like resveratrol), or organic acids (like ascorbic acid) are used as coformers, they not only enhance these physicochemical attributes but also introduce complementary bioactivity. A recent study designed bi-functional analgesic cocrystals by pairing vasodilatory drugs i.e. Pentoxifylline, Clonidine and Linsidomine with nutraceuticals having antioxidant properties (like protocatechuic acid, α-lipoic acid and caffeic acid) in order to target multiple underlying causes of chronic pain, specifically tissue hypoxia and oxidative stress[90,91,92,93].

Patients with altered metabolic profiles (e.g. elderly, diabetic, or liver-compromised patients) often require adjustments in dosage or formulation characteristics. Nutraceutical cocrystals enable such precision by modifying pharmacokinetics to suit the individual's physiology. For example, an antihypertensive drug cocrystallized with vitamin C as a coformer not only improves the drug's solubility but also adds cardiovascular protective effects, for a holistic treatment. Nutraceutical-based cocrystals are adaptive and can easily be fine-tuned based on patient's physiological and pathological state thereby compatible with several comorbidities, age-related physiological changes or dietary deficiencies. For instance, patients with cardiovascular diseases may benefit from a cocrystal combining a statin with omega-3 fatty acid derivatives, offering lipid-lowering activity alongside anti-inflammatory benefits. Similarly, Metformin:Ferulate (Ferulic acid) salt not only manage blood glucose levels but also reduce oxidative stress and vascular inflammation in diabetic patients. Similarly, dual-action cocrystals can help significantly reduce the burden of poly-pharmacy, improving patient compliance and therapeutic success[94,95,96].

10. FUTURE OUTLOOK

The field of drug cocrystallization is rapidly evolving, with artificial intelligence (AI) driving a paradigm shift in coformer prediction and design. Hybrid approaches combining machine learning (ML) with physicochemical models like COSMO-RS have significantly enhanced the accuracy and efficiency of coformer screening. Recent studies employing deep learning frameworks such as graph neural networks trained on structural databases have achieved high predictive performance, while generative models like GEMCODE demonstrate potential for de novo design of cocrystals with desirable pharmaceutical attributes. Despite these advances, notable research gaps persist, including the limited availability of high-quality training datasets, challenges in model interpretability and insufficient experimental validation across diverse APIs. Addressing these challenges through explainable AI and broader chemical datasets will be crucial for translating AI-driven insights into practical formulation strategies[97,98,99,100,101].

Future innovation in drug cocrystallization is expected to center around the rational selection of coformers that not only optimize physicochemical characteristics but also

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complement the therapeutic action of APIs. One promising avenue is the use of nutraceuticals and bioactive phytoconstituents as coformers, offering synergistic effects such as antioxidant or anti-inflammatory activity alongside improved solubility and stability. Moreover, the integration of cocrystals into advanced drug delivery platforms—such as 3D-printed dosage forms, nanoparticulate carriers, and in situ gels—can significantly enhance bioavailability, targeting, and patient adherence. This synergy between crystal engineering and delivery system innovation holds the potential to redefine drug performance metrics, particularly in poorly soluble or low-permeability compounds. Continued research into the pharmacokinetic behavior of cocrystals within such novel delivery matrices will be essential for regulatory acceptance and clinical translation[94,102].

11. CONCLUSION

Using cocrystallization to improve the biopharmaceutical attributes of current APIs is particularly promising since they can overcome the weak physico-chemical characteristics of medicinal molecules. Cocrystals are attracting the attention of researchers since regulatory bodies like the USFDA and EMA have already published guidelines for them. They can facilitate the development of novel pharmaceutical drugs with improved effectiveness and fewer adverse effects. Furthermore, by offering a method for prolonging patent exclusivity, co-crystals can help protect the intellectual property rights of the drug molecule. Despite having many advantageous qualities (such as antioxidants, anti-inflammatory, etc.), being easily patented and being widely accessible over-the-counter, nutraceuticals have not yet been widely used as coformers in cocrystallization. A small number of researches have investigated the cocrystallization of APIs with nutraceuticals in an effort to positively modify the physico-chemical characteristics of APIs, including their solubility, bioavailability, and physical stability.

This review assesses the research studies conducted in the formulation of Drug-Nutraceutical cocrystals & identifies the enhancement of various physico-chemical properties. But there are still a number of obstacles to overcome. Co-crystal synthesis and characterization demand for tailored techniques and insight. For industrial applications, creating production processes that are both scalable and reproducible is crucial. Furthermore, it is necessary to define the regulatory environment for co-crystals in the pharmaceutical sector, guaranteeing appropriate review and approval procedures.

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