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"Cocrystal in pharmaceutical Market in view Regulatory prospective And Intellectual property rights"

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In present time, the Biopharmaceutical Classification System (BCS) II and IV classes have issue of poor water solubility and low bioavailability, account for 90% of novel chemical entities and 40% of medications that are currently on the market. The dissolution rate and solubility of a drug are key factors that affect its gastrointestinal absorption in oral drug delivery system There are various approaches that have been adopted for improving the aqueous solubility of drugs. Some of these approaches are micronisation, solid dispersion, salt formation, self- emulsifying drug delivery system (SEDDS), solubilisations using co-solvents and the use of polymer drug vehicles for delivery of poorly soluble drugs.[1-2]

Most current drugs are administered to patients in the solid state due to factors like cost, stability, and convenience of administration (tablets, capsules, powders). There are two types of solid-state APIs: crystalline and amorphous. A regular repeating arrangement of atoms makes up the organised interior structure of crystalline solids. Solids that are amorphous lack an organised interior structure. An API is frequently prepared in its most thermodynamically stable polymorphic form, which is crystalline, either as a salt or hydrate. The two types of chemicals that make up crystals are single- and multi-component compounds. Although the size of this difference is often minimal, polymorphs differ from one another physically. They also exhibit a hierarchy of stability, with the lowest free energy structure being the most stable and, consequently, least stable.[3]

A pharmaceutical cocrystal is a solid-state form of a drug molecule that is formed by combining two or more different molecular components, typically the drug molecule and a coformer, in a crystal lattice. These components are held together by non-covalent interactions, such as hydrogen bonding, van der Waals forces, and π-π stacking interactions.Pharmaceutical crystals are a subclass of crystals in which one component is a medication molecule (or active pharmaceutical ingredient, or API) and the other is a safe food or drug grade additive (generally regarded as safe, GRAS).[4-8] The crystal lattice of the two components contains hydrogen bonds between them in a predetermined stoichiometric ratio. Pharmacokinetic and physicochemical properties of drug substances, such as solubility and dissolution rate, bioavailability, particle morphology and size, tableting and compaction, melting point, physical form, biochemical and hydration stability, and permeability, have shown significant promise over the past ten years. In this pharmacological cocrystals that have improved solubility and permeability within the same cocrystal, increased the melting point for solid formulation, improved colour performance, photo stability and hydration stability, and a longer half-life.[9]

Pharmaceutical Cocrystals Preformulation and Pharmaceutical Development Aspects:

A crucial stage in this process is the identification of possible supramolecular synthons. Desiraju created the concept of "supramolecular synthon" at the beginning. it as "structural units inside supermolecules which can be generated and/or assembled by known or feasible synthetic procedures involving intermolecular interactions."[10] The **supramolecular synthons technique**, establishes the essential complimentary functional groups of coformers and the suitable functional groups that need be present on APIs in order to produce cocrystals. The most widely used supramolecular synthon pairs can be obtained from the Cambridge Structural Database. (CSD) The selection of potential coformers and the prediction of the results of interactions are made possible by knowledge of synthons**.** [11-12]

Supramolecular synthons have been classified into two categories.

(i) supramolecular homosynthons, in which intermolecular interactions take place between the same functional groups (such as carboxylic acid-carboxylic acid or amide-amide);

(ii) supramolecular heterosynthons, in which intermolecular interactions take place between two different groups (such as carboxylic acid-amide or carboxylic acid-pyridine).

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Computed molecular electrostatic potential surface (MEPS). Using the molecular electrostatic potential between donors and acceptors on the molecular surface, MEPS has been used to forecast cocrystallization and identify compounds that are likely to form cocrystals.

Solution-based pKa valuespKa values are utilised to determine the H-bond donors when designing cocrystals, cocrystal formation typically takes place when the DpKa value is low (0). [14]

Hansen solubility parameters (HSPs)

Drug's miscibility with a coformer can be calculated using HSP . A Ddt (i.e., difference in HSP) of less than 7 MPa 0.5 was shown to be indicative of good cocrystal formation for drug and coformer components.[13]

Lattice energy

It is Computational methods**.** By contrasting the computed energy of the cocrystal lattice with the energy of the two pure phases, lattice energy calculations have been used to forecast the formation of cocrystals. It may be a more thermodynamically stable phase if the predicted lattice energy of the cocrystal is lower than the sum of the calculated lattice energies of the pure components. [14]

Ternary phase diagram (TPD)- computer modelling techniques. TPDs are crystallisation experiments that are particularly useful for figuring out the thermodynamic connections between cocrystals and each of its constituent parts as well as the best methods for preparation. The solubility curves of the drug, coformer, and cocrystal solid phases in the solvent at a certain temperature are typically used to produce TPDs. Binary phase diagrams can also be created from phase diagrams (API–coformer). Thermal analysis data that measure the eutectic mixture and/or eutectic impurities and determine the cocrystal formation zone can be used to assemble binary phase diagrams.[15-16]

Solid-state grinding methods of co-crystal preparation

Co-crystal preparation has made extensive use of the two most prominent solid-state techniques: dry (neat) grinding (DG) and liquid-assisted grinding (LAG). Solid-state grinding, sometimes referred to as mechanochemistry and developed as an alternative to solution-based co-crystal formation techniques, includes both DG and LAG. Compared to solution-based methods, this one is simple, environmentally sustainable, reliable, clean, and likely to produce a yield. [17,18]

1.In dry grinding (DG)

The target drug and the co-former are combined using pressure that is either manually created (using a mortar and pestle) or created mechanically using an automated ball mill. While utilising an automated ball mill, the temperature must be monitored, recorded, and addressed to address any changes that may occur. Typically, this procedure for sample preparation is done at room temperature. Despite its efficiency, simplicity, and other benefits, DG is connected to failure or incomplete conversion to co-crystal and may result in the creation of unstable amorphous due to crystal defect. [19, 20]

2.Liquid-assisted grinding (LAG)

Grinding that is aided by the addition of a very small amount of solvent to the mixture both before and after the grinding process is complete is known as liquid-assisted grinding (LAG). The solvent plays a catalytic role, accelerating and promoting the co-formation. crystal's LAG has been used to create a variety of co-crystals. [21]

Solution-based co-crystal preparation :

Target drug and co-former supersaturation, the nucleation process, and crystal growth are all necessary steps in the co-crystal preparation from solution. To guarantee the thermodynamic stability of the co-crystalline suspension, proper precautions and conditions must be set up (sample containing solution).

1.Evaporative method of co-crystallization :

Evaporative co-crystallization (ECC) has been widely employed to generate co-crystals. The co-crystalline mixture concentration in the solution increases as the solvent volume decreases during evaporation, leading to the super-saturation. ECC is a reliable and favoured method for creating single crystals of high quality suitable for single X-ray diffraction. To maintain reproductivity, dependability of the co-crystal product, and consistency between batches, atmospheric parameters (temperature and pressure) must remain constant during the experiment. Accelerated cocrystallization results from the fast rate of evaporation. This was connected, though, to the growth of unstable/metastable crystals. As a result,

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it is advised to let the solvent evaporate gradually. [22]

2. Ant solvent method:

Ant solvent crystallisation, which is carried out in semibatch or continuous production processes, has been deemed an excellent method to manage the quality, particle size, and characteristics of cocrystals. Antisolvent is added during the crystallisation process to reduce the solubility of the cocrystals until supersaturation is reached, which causes the cocrystals to precipitate. As a result, it's important to select a miscible solvent mixture where the cocrystal has a low solubility in the weak solvent. Although the content of the solvent may have an impact on the solubility of the cocrystal and individual components, the ratio of the cosolvent can have a substantial impact on the yield of cocrystals[23-27].

3. Cooling crystallization :

A common technique for creating large-scale, pure crystals is cooling crystallisation. The distribution size, purity, morphology, and crystal polymorphism in this method are dependent on the local supersaturation, which is governed by the process variables, such as the conversion of mass and heat. [28]In order to make cocrystals, these variables must be properly controlled in accordance with a number of solid-liquid equilibria. The operational region of the crystallisation process is dependent on the cocrystal's stoichiometry and thermodynamic stability zone at the start and end temperatures. Many studies have demonstrated the efficacy of this technology for the scale-up production of crystals. [29-32]

4. Reaction cocrystallization :

When the cocrystal components have various solubilities, reaction cocrystallization can be used to make the cocrystals. Nonstoichiometric reactants are combined to form cocrystal supersaturated solutions, which precipitate as cocrystals. The ability of reactants to reduce the solubility of cocrystals is used in this method to regulate the nucleation and development of cocrystals[33].

5. Slurry conversion:

The solvent must be supplemented with extra cocrystal components in order to use this solution-mediated phase transformation method. To encourage the nucleation and growth of cocrystals, each component gradually dissolves and forms a complex during the slurry. As cocrystals form, the reactant concentrations drop, resulting in under saturation (relative to the reactants), which allows the cocrystal components to continue to dissolve. The ternary phase diagram, which directs cocrystal super saturation generation, controls the operational range of the component's concentration and temperature.

6. Hot Melt Extrusion:

Extrusion is a great way to produce cocrystals because it involves excellent surface interactions and extremely effective mixing. With this method, no solvent was used to produce the co-crystals. The approach was primarily chosen based on the compound's thermodynamic stability. Four models for the creation of crystals of cocrystals were used to study this technique. Often performed at lower temperatures, the solvent drop extrusion technique is utilised to optimise and increase the process's adaptability. Kevin et al. created carbamazepine-nicotinamide cocrystals using the hot melt extrusion process. API and coformer are continuously cocrystallizing in the twin extruder. Continuous mixture adding raises the temperature of the barrel as well. [34]

7.Ultrasound assisted solution crystallization:

An ultrasound-assisted remedy For the creation of nanocrystals, cocrystallization The sonochemical method is frequently employed. In this method, API and cocrystal former are dissolved in a solvent simultaneously, and the resulting solution is then maintained in a sonoreactor to make it turbid. To keep the sonicator's temperature consistent and avoid fragmentation, cold water is provided during sonication. The solution is allowed to dry overnight. This technique produced pure cocrystals, and an X-ray diffraction analysis can be used to determine the purity of the crystals. [35]

8.Spray Drying Technique:

In this method, the solvent is vaporised from the drug and coformer solution or suspension before the cocrystals are formed. This technology is the most popular since it uses a quick, continuous, and one-step approach. In order to prepare and scale up cocrystals, a special environment will be provided via the spray drying method. [36 37].

9.Freeze-drying:

A chemical solution is created, quickly frozen, and then held under a strong vacuum, which

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causes the solvent to sublime. This process is known as freeze-drying. The remaining solute congeals as a low density, frequently amorphous powder. Although amorphous materials are often prepared using the freeze-drying procedure, if the material's glass transition temperature is at or below ambient temperature, it may spontaneously crystallise. The use of freeze-drying as a method of cocrystallization is justified because it makes it possible to create a solid amorphous mixture of two coformers from which a cocrystal can form without encountering the kinetic barrier of the presence of crystalline seeds from the two cocrystal formers. [38]

Cocrystal Characterization:

Physical parameters of cocrystals are determined by using technique such as the melting point apparatus, differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermo gravimetric analysis (TGA), and microscopy[40-41]. Structural properties of cocrystals are characterized by using single crystal X-ray diffraction (SXRD), Powder X-ray diffraction (PXRD), infrared spectroscopy, Raman spectroscopy, and solid-state nuclear magnetic resonance.[42-43] The main method for confirming the production of cocrystals is XRD. The XRD pattern offers a distinctive diffraction pattern that is representative of a specific solid structure[44] .Hot stage microscopy (HSM) can also be utilised to analyse the thermal behaviour and phase transition of solid-phase materials [45]. Vibrational spectroscopic techniques such as IR, Raman, and Terahertz timedomain-spectroscopy are used to predict the chemical structure and hydrogen bonding between the coformer and API. [46-48]. The microscopic examination of solid-phase characteristics, such as crystal size, shape, and surface characteristics, is done using scanning electron microscopy (SEM). Furthermore, solid-phase compound surfaces can be characterised using atomic force microscopy (AFM) [49]. SCXRD is used to determine the structure of cocrystals at the atomic level (e.g., unit-cell dimensions and crystallographic space groups) (e.g., unit-cell dimensions and crystallographic space groups). It also provides complete 3D structural details and atomic locations. An important requirement from the viewpoints of intellectual property and regulatory requirements is the identification of the solid-state structure, Physical properties such melting, crystallisation, sublimation, breakdown, solid-state transitions, and volatile investigated by thermal analysis technique such as DSC, DTA, and TGA [50]. ssNMR and other cutting-edge spectroscopic methods are frequently used in conjunction with single-crystal XRD to characterise pharmaceutical solid forms. Cocrystals and salts can be distinguished from one another using ssNMR, which identifies hydrogen bonds, local conformational changes between cocrystals, and proton transfer in salt formation . By analysing 1H-1H, 1H-13C, and 19F-13C coupling, ssNMR also offers a valuable understanding of hydrogen bonding and local conformational changes [51-52].

Patents on Co-Crystals:

The use of pharmaceutical co-crystals has increased significantly, and several research publications and patent applications have been submitted worldwide.

Co-crystals and multi-drug co-crystals have been the subject of several authorised patents as of this writing. Table 2 lists some of the recently approved pharmaceutical co-crystal formulations as well as a list of approved pharmaceutical co-crystal patents in the United States, Europe, and other countries (including the entire world). [53]

Commercially available cocrystals:

1. SEGLENTIS®

SEGLENTIS contains tramadol hydrochloride, an opioid agonist, and celecoxib, a no steroidal anti-inflammatory drug, and is indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

2.Aripiprazole

Aripiprazole is a co-crystal formulation sold under the trade name Abilify®. Aripiprazole and fumaric acid are the main ingredients in Abilify. Aripiprazole is a psychoactive medication that can be used to treat schizophrenia. [54]

3.Steglatro

Under the trade name SteglatroTM, the Food and Drug Administration (USFDA) has approved the ertugliflozin co-crystal formulation (ertugliflozin cocrystal with 5-oxo-proline).[55]

4.Entresto

A multidrug co-crystal formulation of sacubitril and valsartan (brand name: Entresto, Novartis) was approved by the US Food and Drug

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Administration (FDA) on July 7, 2015, to lower the risk of cardiovascular disease and chronic heart failure. Fast-track review was used to approve the novel oral combination Entresto. [56]

5.Lexapro

Escitalopram is a component of the co-crystal formulation known as Lexapro, which was given approval in 2009 to treat serious depression and anxiety disorders.[57]

6.Suglat® (Ipragliflozin: L-proline)

Ipragliflozin, a sodiumglucose co-transporter-2 (SGLT2) inhibitor, was created as a 1:1 molecular ratio co-crystal with L-Proline by Astellas Pharma and Kotobuki Pharmaceuticals. In Japan, the cocrystal formulation is offered under the brand name Suglat® after receiving approval. [58]

7.Odomzo® Co-crystal of sonidegib and phosphoric acid was formulated for Treatment of cancers in 2015 by company Novartis/Sun Pharma.

Composition patents issued in the USA for pharmaceutical cocrystals

Patent no	Date	Main content	Assignee	Ref.
US20170101433 A1	13 Apr, 2017	Co-crystal of progesterone and a co-former selected from the group consisting of vanillic acid, benzoic acid, salicylic acid, cinnamic acid,	Amri Sci. Llc.	59
US20170224724 A1	10 Aug, 2017	Co-crystal (ICC) of lithium with salicylic acid and l-proline	University Of South Florida	60
US20170044176 A1	16 Feb, 2017	Cocrystal of tiotropium bromide and lactose monohydrate	Euticals Spa	61
US8163790	24 Apr, 2012	Metronidazole cocrystals with gentisic acid and gallic acid (specific x-ray reflections in each case) and a cocrystal of imipramine HCl and (+)-camphoric acid	New Form Pharmaceuticals, Inc.	62
US8124603	28 Feb, 2012	Meloxicam with various carboxylic acids, aliphatic and aromatic, and maltol and ethyl maltol	Thar Pharmaceutical	63
US8097592	17 Jan, 2012	SGLT-2 Inhibitor, l-proline cocrystal	Astellas Pharma Inc., Ltd.	64
US8080580	20 December 2011	SGLT-2 inhibitors, l-proline and pyroglutamic acid cocrystals	Pfizer Inc.	65
US8058437	15 November 2011	(Pyrroloquinoxalinyl)pyrazinecarbo-hydrazide, oxalic acid co-crystal	Novelix Pharmaceuticals, Inc.	66

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US8039475	18 October 2011	Telaprevir; salicylic acid, variable stoichiometry	Vertex Pharmaceuticals, Inc	67
US8003700	23 August 2011	Cochicine; solid complexes, malic acid cocrystal	Mutual Pharmaceutical Co., Inc.	68
US7935817	3 May 2011	Adefovir dipivoxil; nicotinamide and salicylamide conformers	Apotex Pharmachem Inc	69
US7691827	6 April 2010	Gemcitabine: a prodrug cocrystallized with aromatic sulfonic acid, hydrate	Eli Lilly & Co.	70
EP3240575 A1	8 Nov, 2017	co-crystal of carfilzomib with maleic acid	Dr. Reddy's Laboratories Ltd.	71
EP3210975 A1	30 Aug, 2017	Cocrystals of Lorcaserin hydrochloride and an organic diacid	Enantia, S.L	72
EP1608339B1	21 Mar, 2012	Celecoxib cocrystal with nicotinamide	McNeil PPC	73
EP2288606B1	15 Feb, 2012	Rivaroxaban cocrystal with malonic acid	Bayer Pharma Ag	74
EP2114924B1	25 Jan, 2012	Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvate	Vertex Pharmaceuticals Inc.	75
EP2300472B1	18 Jan, 2012	Glucocorticoid analogs, phosphoric acid and acetic acid cocrystals	Boehringer Ingelheim Intl. GmBH	76
EP2334687B1	4 Jan, 2012	SGLT-2 inhibitors, 1-proline and	Pfizer Inc	77

Summary of cocrystal products currently in clinical trials[86]

Drug	Phase	Company	Clinical trial identifier
TAK-020 (TAK-020–gentisic acid)	Phase I	Takeda Pharmaceuticals	NCT02723201
E-58425 (tramadol hydrochloride–celecoxib)	Phase III	Esteve	NCT03108482
T121E01F/T121E02F (zoledronic acid cocrystal)	'Phase III ready'	Thar Pharmaceuticals	NCT01721993
CC-31244 (non-nucleoside polymerase inhibitor)	Phase IIIa	Cocrystal Pharma	NCT0276075

Regulatory Perspectives

To clarify the status of co-crystals in their different regions, regulatory authorities like the European Medicines Agency (EMA) and the United States Food and Drug Administration (USFDA) have developed regulatory recommendations. Cocrystal research has advanced significantly in the previous ten years; a small number of cocrystal-related patents have already been issued. An invention must meet the three requirements of **novelty, non-obviousness, and utility or usefulness in order to be patentable**.[87-88]

In 2013, the USFDA published the first set of regulations for pharmaceutical co-crystals; these regulations classed pharmaceutical co-crystals as drug product intermediates and handled them similarly to APIexcipient molecular complexes. The text further stipulated that: • The API and the

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co-former should be in neutral states, and their interactions should not be covalent or ionic; and
• The value of pKa should be less than 1, which is defined as pKa [pKa (base) - pKa (acid)] 1.
Before reaching the site of pharmacological activity, the API and the co-former should totally separate.
The FDA's updated regulations, which were issued in 2016, identify pharmaceutical co-crystals as a particular case of solvates and hydrates and place them in a regulatory category equivalent to that of an API polymorph. Moreover, FDA required an invitro study based on solubility and/or dissolution is typically regarded as sufficient to show that the active medication entirely separates from the co-former.[89-90]

The USFDA and EMA classification of Pharmaceutical co-crystals is summarised in Table

Regulatory considerations	Food & Drug Administration guidance (2013 & 2016)	European Medicines Agency reflection paper (2015)
Regulatory category	Polymorph of the Active Pharmaceutical Ingredient	Active Pharmaceutical Ingredient
Composition	Active Pharmaceutical Ingredient & a food or drug grade co-former	Active Pharmaceutical Ingredient and co-former in fixed stoichiometric ratio
Interaction in crystal	Non-ionic/non-covalent interactions	Non-ionic/non-covalent interactions
Co-former role	Excipient	Reagent
Drug Master File/Active Substance Master File requirement	No	Required for New Active Substance registration

Concluding Remarks and Future Perspectives:

Cocrystals have been shown to be alternate solid forms with potentially alluring advantages, but screening techniques, manufacturing scale-up routes, and approval procedures are still problematic. There is a need for clearer, more rational guidelines in order to expand opportunities for the prospective future market for medicinal cocrystals, whose current regulatory approaches diverge between the FDA and EMA. Cocrystallization is one promising field for the development of new medications by changing important pharmaceutical qualities, such as particle size and shape hygroscopicity, melting point, and solubility, as well as the improvement of in vivo bioavailability. The success of the creation of pharmaceutical cocrystal drug products will be increased by careful rationalisation of cocrystal design and simplified manufacturing alternatives.

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