A Review about Regulatory Status and Recent Patents of Pharmaceutical Co-Crystals

Arun Kumar, Sandeep Kumar, Arun Nanda*

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, India.

Introduction

Pharmaceutical co-crystals have established a new paradigm in the solid-state modification. The formation of API co-crystal offers a wide range of physical and chemical enhancements to the properties of drugs without altering their chemical nature, thereby maintaining its pharmaceutical importance as such.1 This is evident from the fact that regulatory bodies like United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA) have published regulatory guidelines to clarify the status of co-crystals in their respective regions. Pharmaceutical and Biotechnology companies rely upon intellectual protection for safeguarding their products. In order to maintain revenues generated through these products as a means to recover the resources and money spent on research and development, the presence of proper regulatory guidelines is expected to significantly affect the development and quality control as well as intellectual properties aspects of pharmaceutical cocrystals and their formulations.2

However, the concern that remains unanswered is whether the standard development and manufacturing processes that were initially designed for salt-based formulations can also be used for co-crystal based formulations in order to achieve the desired product quality that is required to ensure the safety and efficacy.3 Moreover, from regulatory perspective the addition of another component to the drug formulation could mandate additional bioequivalence, clinical and toxicity studies.

This article focuses on listing recent developments regarding regulatory status of co-crystals in different regulatory regions, the effect of these regulatory guidelines and intellectual protection in the field of crystal engineering. Another point to be probed is whether co-crystals are eligible for patent protection or not as per the literature and guidelines available on pharmaceutically acceptable co-crystals.

Pharmaceutical Co-Crystals

Poor solubility has been a crucial issue in the development of a pharmaceutical dosage form. Amorphous solids may be considered as a good choice but these solids have their own limitations related to stability.4 The composition and the arrangement of molecules/ions in a crystal lattice directly affects the crystal properties, it means that exerting control over the composition by selecting a co-former from a wide range can lead to co-crystals of desired physicochemical properties. This was the reason crystal engineering gained impetus in pharmaceuticals for the enhancement of stability/solubility of pharmaceutical formulations.5 Co-crystals can be made for both complex drugs containing sensitive functional groups as well as for drugs containing non-ionizable moieties and that is the unique advantage of co-crystals over salts. The other key advantages of co-crystals are that co-former modifies only the physicochemical properties of drug without altering the molecular structure and pharmacological properties of the drug.6

Keywords:
- Pharmaceutical Co-crystals
- Crystal Engineering
- Regulatory guidelines
- Patents

Article info

Article History:
Received: 27 February 2018
Revised: 24 April 2018
Accepted: 20 May 2018
ePublished: 29 August 2018

Abstract

Pharmaceutical Co-crystals are not new, they have gained much attention since the last decade among scientists and pharmaceutical industry. Pharmaceutical co-crystals are multicomponent systems composed of two or more molecules and held together by non-covalent interactions. The development of pharmaceutical co-crystals, a new solid crystalline form, offer superior physico-chemical properties (such as melting point, stability, solubility, permeability, bioavailability, taste masking, etc.) without altering the pharmacological properties. Recently, with the upsurge in the growth of Pharmaceutical co-crystals, the major concern is over the regulatory status of co-crystals. With the new guidelines from United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA), the status has become even more complicated due to significantly different opinions. This review highlights whether co-crystals fulfil the requirements for the grant of a patent or not and how cocrystals are going to affect the present scenario of pharmaceuticals.

*Corresponding author: Arun Nanda, Tel: +919896294630, Email: an.pharmsciences@mdurohtak.ac.in
© 2018 The Authors. This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited. No permission is required from the authors or the publishers.
Cocrystals are a long known but understudied class of crystalline solids. In 1844, Wohler was the first to obtain a co-crystal of the 1:1 ratio between Benzoquinone and Hydroquinone (Quinhydrone). Desiraju in 1989 defined crystal engineering as “the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties.” However, pharmaceutical co-crystals have attracted interest from scientists in the past decade and now much of work has been done in this field, mainly because co-crystallization utilizes non-covalent interactions and supramolecular synthons to control the organisation of molecules inside the crystal lattice, co-crystals possess better thermodynamic stability, purity and processing characteristics over amorphous solids.

In 2004, Almarsson and Zaworotko proposed the least controversial definition of co-crystals as “co-crystals are those that are formed between an active pharmaceutical ingredient (API) and a co-former also called as crystal former (CF), which under ambient conditions are solids. This definition is not limited to two components, that the co-crystal can be multi-component”. The components in the co-crystal interact by hydrogen bonding or other non-ionic and non-covalent interactions such as halogen or π-π interactions. In 2011, a bilateral meeting jointly sponsored by the Indo–U.S. Science and Technology Forum (IUSSTF) was held on Pharmaceutical Cocrystals and Polymorphs where meeting a generally accepted definition of co-crystals was evolved which reads as follows “Cocrystals are solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts”. USFDA defined that cocrystals are crystalline materials which are composed of two or more molecules in the same crystalline lattice and associated by non-ionic and non-covalent bonds.

Pharmaceutical co-crystals belong to a subclass of co-crystals wherein one of the components is a biologically active substance (an API) while the other one the co-former is drug or food grade substance (generally regarded as safe). Inside the crystal lattice the two components interact through non-covalent interactions such as hydrogen bonding in fixed stoichiometric ratio. The foundation of crystal engineering lies in the concept of supramolecular chemistry. The basic tenet of supramolecular chemistry is the molecular recognition between complementary molecular fragments giving rise to self-organization of molecules to give a supramolecular function. Co-crystallization has been shown to significantly modify the physicochemical properties of drug substances such as the, permeability, bioavailability, solubility and dissolution rate, compaction and tableting, physical form, biochemical and hydration stability, melting point, etc. Selection of suitable co-formers and screening of co-crystals for a drug are the main challenges to overcome during the process of cocrystal development. Selection of co-formers is mainly done by researchers using theoretical or experimental approaches. Different approaches i.e. hydrogen bonding propensity, Cambridge Structure Database, supramolecular synthons, ∆pKa values, Fabine’s method, COSMO-RS screening, Hansen solubility parameters, virtual cocrystal screening, thermal methods (including DSC screening, hot stage microscopy and saturation method) and others methods are reported in the literature by the scientists for the selection of the appropriate co-former for a drug and screening of cocrystals.

Academics and scientists reported various methods (such as solution based, grinding, and other advanced methods freeze drying, spray drying, hot melt extrusion, supercritical carbon dioxide processing, ultrasound crystallization and microfluidic jet dispersion) for the synthesis of cocrystals with their pros and cons. Bavishi and Borkhataria described the “Spring and Parachute” concept for better understanding in the improvement of solubility and dissolution rate of drug. Different characterization techniques such as structural analysis (crystallographic studies, Hirshfeld surface analysis and spectroscopic characterization), thermal analysis (Differential scanning calorimetry, thermogravimetric analysis and hot stage microscopy) and pharmaceutical characterizations (solubility and dissolution profile, stability, bioavailability and pharmacokinetic studies) have been used for determining the successful synthesis and pharmaceutical utility of cocrystals.

A co-crystal is also possible between two biologically active molecules that is drug: drug co-crystal. The motive behind multidrug cocrystals is towards developing combination therapies, prevention of multi-drug resistance, synergistically increasing the action of drugs, reducing side effects, etc. Bhatt et al., reported a co-crystal between Lamivudine and Zidovudine (both anti-viral drugs active against HIV).

**Regulatory prospects and patentability issues of Co-Crystals**

Once a pharmaceutical cocrystal with promising results is developed, the next step would be gaining regulatory approval so that it can be brought to market. However, the lack of clear regulatory guidelines is a major issue to tackle with. Over the last decade, cocrystal development has seen enormous growth, there are even few patents granted for cocrystals. For an invention, in order to be patentable, the invention must fulfil the three conditions such as novelty, non-obviousness and utility or usefulness.

**Novelty**

Desiraju in his book “Pharmaceutical salts and cocrystals: retrospect and prospects” mentioned that pharmaceutical co-crystals are new composition of matter and hence should satisfy the requirement of novelty for the grant of patent. Andrew Trask in his article titled "An Overview of Pharmaceutical Cocrystals as Intellectual Property" also stated that pharmaceutical
co-crystals should satisfy the novelty condition as equally as salts. Both Desiraju and Andrew emphasised that since co-former screening is a daunting work and co-formers are selected from a huge official list of GRAS compounds and the result of co-crystallization is not easily predictable, co-crystals may or may not be formed. Apart from this, the properties of the synthesized co-crystals cannot be anticipated. But the situation is completely different, FDA didn’t even consider co-crystals in the same class as that of salts or polymorphs.39

Non-obviousness
Non-obviousness means that if someone skilled in the relevant field of technology and familiar with its subject matter invented it with comparative ease; such an “invention” would be novel but obvious to that person. Desiraju described that unlike salt formation wherein an acid is necessary to form a salt with a base, the identification of a co-former is hardly an ever routine.38 According to Trask, in spite of a number of co-crystals screening methods available, there is no confirmed way to predict whether two molecules will form a hydrogen bond and a co-crystal will be formed. There are a lot of factors that govern the co-crystallization process and still there is a need to better understanding of this process. Moreover, co-crystal structure cannot be predicted from the available sources. Hence co-crystals well satisfy the Non-obviousness criteria too.39

Utility
In case of Pharmaceutical co-crystals, the only criteria that needs to be demonstrated in order to obtain a patent is utility or application of the invention. Co-crystals offer opportunities similar to that of polymorphs. They are clearly new substances, problems of inherent anticipation are not likely to arise so often and more of them can be made for any given API, expanding the pharmaceutical space around it and consequently the types of advantageous properties that may be accessed.38 As per Trask, co-crystal of an API shares the same patentable therapeutic utility as its parent API. The enormous research on co-crystals in the past decade indicates that co-crystals offer vast opportunities for enhancement of the properties of an API, which in turn increases its utility and hence also the chances of patentability.39

Regulatory Perspectives
USFDA was the first regulatory body to publish guidelines for pharmaceutical co-crystals in 2013; the guidance classified Pharmaceutical co-crystals as drug product intermediate and treated them similar to API-excipient molecular complexes. Further the document stated that:

- The API and the co-former should completely dissociate before reaching the site of pharmacological activity.12
- The API and the co-former should completely dissociate before reaching the site of pharmacological activity.12

The revised guidelines of FDA published in 2016, classify the pharmaceutical co-crystals as a special case of solvates and hydrates and placed pharmaceutical co-crystals in the regulatory classification similar to that of a polymorph of the API. Additionally, FDA required an in-vitro evaluation based on dissolution and/or solubility is generally considered sufficient to demonstrate that the active drug dissociates completely from the co-former.13 EMA’s opinion on Pharmaceutical co-crystals differs considerably from that of FDA. EMA published a paper in 2014 about cocrystals and placed co-crystals in the same class as that of salts. The regulations also classify that co-crystals are eligible for generic application in the same way as salts. For a co-crystal to be considered as New Active Substance status (NAS), the co-crystals should demonstrate the difference in efficacy and/or safety with respect to that of API. NAS status for other routes of administration will be dependent on the therapeutic moiety that is present at the site of pharmacological action when compared to that of the authorised product.40 The USFDA and EMA classification of Pharmaceutical co-crystals is summarised in Table 1.

Patents on Co-Crystals: Case Studies
Over the past decade, Pharmaceutical co-crystals have seen enormous growth and a large number of research papers and patents have been filed all over the world and till date, a number of patents related to co-crystals and multi-drug co-crystals have been approved. Some of the recently approved pharmaceutical co-crystal formulations and list of approved patents on pharmaceutical co-crystals in USA, Europe, International (worldwide) and multi-drug co-crystals patents have been enlisted in the Table 2, Table 3, Table 4 and Table 5 respectively.

Entresto
The US Food and Drug Administration (FDA) on July 7, 2015, approved a multidrug co-crystal formulation of sacubitril and valsartan (brand name Entresto, Novartis) to reduce the risk for cardiovascular and chronic heart failure. Entresto was a new oral combination approved through fast-track review.41

Lexapro
Lexapro is a co-crystal formulation composed of escitalopram and was approved in 2009 under the brand name Lexapro, for the treatment of major depressive and anxiety disorders.42

Steglatro
The Food and Drug Administration (USFDA) has approved Ertugliflozin co-crystal formulation (Ertugliflozin cocystal with 5-oxo-proline) under the brand name Steglatro™.43,44
**Suglat® (Ipragliflozin: L-proline)**

An Ipragliflozin: L-Proline co-crystal of the molecular ratio 1:1 was developed by Astellas Pharma and Kotobuki Pharmaceuticals. Ipragliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor. The co-crystal formulation was approved and is available under the trade name Suglat® in Japan.\(^{45,46}\)

---

**Aripiprazole**

Aripiprazole is a co-crystal formulation available in the market under the brand name Abilify®, Abilify consists aripiprazole and fumaric acid. Aripiprazole is a psychotropic drug useful for the treatment of schizophrenia.\(^{47}\)

---

**Tramadol-Celecoxib (1:1) Cocrystal**

E-58425 comprising celecoxib and tramadol (1:1) was developed by Enantia and Esteve, R&D, Spain, and patented by Laboratorios Del. This is an example of multidrug cocrystal, which is under clinical development. Synergistic action between its components will help to achieve the therapeutic benefits at lower and tolerable doses of each component. A phase II proof-of-concept study in acute postoperative pain has shown that the cocrystals demonstrated superior efficacy and safety over both placebo and a standard. The co-crystal based formulation is currently in phase-III of clinical trials.\(^{48-50}\) Some other patents about the novel cocrystals of tiotropium bromide and ticagrelor drugs have also been granted to Boehringer Ingelheim Pharma Gmbh Co and Astrazeneca respectively.\(^{51}\)

---

**Table 1. Comparison between United States Food & Drug Administration and European Medicines Agency guidelines\(^3\)**

| 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 |
| New Chemical Entity /New Active Substance Registration | No | Possible if shown difference in efficacy/safety |
| Similarity with Active Pharmaceutical Ingredient | Similar | Similar unless demonstrated different efficacy/safety |
| Classification            | Polymorph of Active Pharmaceutical Ingredient | Salts of Active Pharmaceutical Ingredient |
| Cocystal and salt         | Differences in interaction and regulatory pathways | Regulation dependent on efficacy/safety |
| Drug Master File/Active Substance Master File requirement | No | Required for New Active Substance registration |

---

**TAK-020—Gentisic acid Co-crystals**

Takeda Pharmaceuticals developed a new co-crystal-based formulation named TAK-020 developed for the treatment of rheumatoid arthritis (Bruton’s tyrosine kinase inhibitor). The co-crystal has completed phase-I clinical trials.\(^{46}\)

---

**Table 2. Composition patents issued in the USA for pharmaceutical cocrystals\(^2\)**

| US Patent No. | Date of issue | Assignee | Compound(s) | Ref. |
|---------------|---------------|----------|-------------|------|
| US6001996     | 14 Dec, 1999  | Eli Lilly & Co., Inc. | Complexes of (carba)cephalosporins with parabens | 52   |
| US7446107     | 4 Nov, 2008   | Transform Pharmaceuticals, Inc. | Itraconazole; cocrystals with carboxylic acid | 53   |
| US7625910     | 1 Dec, 2009   | Astra Zeneca AB | AZD1152; a phosphate prodrug and maleic acid cocrystal | 54   |
| US8097592     | 17 Jan, 2012  | Astellas Pharma Inc., Kotobuki Pharmaceutical Co. Ltd. | SGLT-2 Inhibitor, I-proline cocrystal | 55   |
| US8124603     | 28 Feb, 2012  | Thar Pharmaceutical | Meloxicam with various carboxylic acids, aliphatic and aromatic, and maltol and ethyl maltol | 56   |
| US8163790     | 24 Apr, 2012  | New Form Pharmaceuticals, Inc. | Metronidazole cocrystals with gentisic acid and gallic acid (specific x-ray reflections in each case) and a cocrystal of imipramine HCl and (+)-camphoric acid | 57   |
| US20170044176 | 16 Feb, 2017  | Euticals Spa | Co-cystal of tiotropium bromide and lactose monohydrate | 58   |
| US20170224724 | 10 Aug, 2017  | University Of South Florida | Co-crystal (ICC) of lithium with salicylic acid and 1-proline | 59   |
| US20170101433 | 13 Apr, 2017  | Amri Sci. Llc. | Co-crystal of progesterone and a co-former selected from the group consisting of vanillic acid, benzoic acid, salicylic acid, cinnamic acid, and vanillin. | 60   |
Recent Regulatory Updates on Cocrystals

### Table 3. European patents on Co-Crystals

| Patent no. | Date of issue | Assignee | Compounds | Ref. |
|------------|---------------|----------|-----------|------|
| EP17553888B1 | 6 Oct, 2010 | TransForm Pharmaceuticals, Inc. | Mixed cocrystals of modafinil | 61 |
| EP2185546B1 | 26 Oct, 2011 | Vertex Pharmaceuticals, Inc. | Cocrystals and pharmaceutical compositions, telaprevir (VX-950) | 62 |
| EP2334687B1 | 4 Jan, 2012 | Pfizer Inc. | SGLT-2 inhibitors, l-proline and pyroglutamic acid cocrystals | 63 |
| EP2300472B1 | 18 Jan, 2012 | Boehringer Ingelheim Intl. Gmbh | Glucocorticoid analogs, phosphoric acid and acetic acid cocrystals | 64 |
| EP2114924B1 | 25 Jan, 2012 | Vertex Pharmaceuticals Inc. | Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvates | 65 |
| EP2288606B1 | 15 Feb, 2012 | McNeil PPC | Rivaroxaban cocrystal with maleic acid | 66 |
| EP1608339B1 | 21 Mar, 2012 | Pfizer Inc. | SGLT-2 inhibitors, l-proline and pyroglutamic acid cocrystals | 67 |
| EP2114924B1 | 25 Jan, 2012 | Vertex Pharmaceuticals Inc. | Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvates | 68 |
| EP3210975 A1 | 30 Aug, 2017 | Aurobindo Pharma Limited | dl-proline cocrystal of dapagliflozin | 69 |
| EP3240575 A1 | 8 Nov, 2017 | Intra-Cellular Therapies, Inc. | Co-crystal forms of 1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3’ 4’:5]pyrrolo[1,2,3-de]quinolin-8-yl)-butan-1-one and isonicotinamide and nicotinamide. | 70 |
| EP1608339B1 | 21 Jan, 2012 | McNeil PPC | Celecoxib cocrystal with nicotinamide | 71 |
| EP3210975 A1 | 30 Aug, 2017 | Enantia, S.L. | Cocrystals of Lorcaserin hydrochloride and an organic diacid | 72 |
| EP3204057 A1 | 8 Nov, 2017 | Dr. Reddy’s Laboratories Ltd. | Co-crystal of carfilzomib with maleic acid | 73 |

### Table 4. International patents on Co-Crystals

| Patent no. | Date of issue | Assignee | Compounds | Ref. |
|------------|---------------|----------|-----------|------|
| WO2017191539 A1 | 9 Nov, 2017 | Aurobindo Pharma Limited | dl-proline cocrystal of dapagliflozin | 61 |
| WO2017172811 A1 | 5 Oct, 2017 | Intra-Cellular Therapies, Inc. | Co-crystal forms of 1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3’ 4’:5]pyrrolo[1,2,3-de]quinolin-8-yl)-butan-1-one and isonicotinamide and nicotinamide. | 62 |
| WO2017144598 A1 | 31 Aug, 2017 | Enantia, S.L. | Cocrystals of Lorcaserin hydrochloride and an organic diacid | 63 |
| WO2017115284 A1 | 6 Jul 2017 | Pharmaceuticals Pvt. Ltd. | Adipic acid co-crystal of Agomelatine | 64 |
| WO2016156127 A1 | 6 Oct 2016 | Ratiopharm Gmbh | Co-crystal of ibritinib and carboxylic acid | 65 |

### Table 5. Patents on multi-drug Co-Crystals

| Drug combination | Therapeutic category | Refs. |
|------------------|----------------------|------|
| ASA–theanine     | NSAID and psychoactive | 75   |
| Ciprofloxacin–dithianon | Fungicides | 76   |
| Ciprofloxacin and norfloxacin with various co-crystal formers | Antibacterial | 77   |
| Mesalamine with alpha amino acids, flavones, and nutraceuticals | Anti-inflammatory | 78   |
| Metformin–oleylethanolamide | Antidiabetic and anti-obesity | 79   |
| Quercetin–metformin | Antioxidant and antidiabetic | 80   |

**Co-crystals and Evergreening of Patents**

Ever-Greening and follow on patent are used to refer the patents that are filled to protect the additional aspects of further improvements to an invention. This provision of follow on patents to an existing invention was included in law so as to encourage further research as a means to obtain pharmaceutical products that are much safer and effective. While the terms “ever-greening patent” and “follow-on patent” are both used to refer to patents that protect pharmaceutical formulations, new forms of active agents, processes for manufacturing active agents, new uses for pharmaceutical products, new combinations of active agents, new dosing regimens, most of the pharmaceutical companies have ill practiced in this provision and have created picket fences of minor improvements filled over the parent patent and hence successfully thwarting any generic entry in the market and maintaining their monopoly for extended periods of time. While, Co-crystallisation is an approach that results in drug products that seem to satisfy the conditions of novelty, non-obviousness and utility but it may definitely stimulate investigation of older APIs for new benefits...
and this may in turn lead to ever greening of existing drug patents.81

Conclusion
Co-crystallization is a flourishing approach with direct application to the pharmaceutical industry. It is quite evident from the amount of interest shown by both academia and pharmaceutical industry that in near future pharmaceutical cocrystals will be one of the viable and important solid forms of pharmaceuticals that should be available in the market. The value of co-crystals to the pharmaceutical industry should become clearer, particularly with respect to several relevant legal and regulatory issues, as products containing cocrystal technology emerge from pharmaceutical development pipelines into the market. It will also lead to screening of older API’s to see new benefits and improvements of existing drugs. Co-crystal formation offers tremendous scope for controlled modification of the key pharmaceutical properties such as dissolution rate, solubility, compressibility, melting point, stability, bioavailability and permeability. There is a need to explore into an understanding of cocrystallization mechanism, in-vivo behaviour of cocrystal for better therapeutics and other unanswered questions like polymorphic transformation, the concepts of supramolecular synthesis, and crystal engineering remain largely underexploited. Pharmaceutical cocrystals generally appear patentable when measured against the criteria of novelty, utility, and non-obviousness as evident from the fact that number of patents filed throughout the world by various pharmaceutical industries and research groups are also increasing at a fast pace. The challenges that lie ahead include scaling up the production of the pharmaceutical cocrystals, preceded by discovery of new scale up methods, and high throughput screening of the possible co-crystal with various co-formers and their polymorphs.

Acknowledgments
Authors thank Maharshi Dayanand University, Rohtak and University Grant Commission, New Delhi for providing University Research Fellowship and Basic Scientific Research Fellowship respectively, for working in the project.

Ethical Issues
Not applicable.

Conflict of Interest
The authors declare no conflict of interests.

References
1. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. J Pharm Sci 2006;95(3):499-516. doi: 10.1002/jps.20578
2. Almarsson O, Peterson ML, Zaworotko M. The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. Pharm Pat Anal 2012;1(3):313-27. doi: 10.4155/ppa.12.29
3. Izutsu KI, Koide T, Takata N, Ikeda Y, Ono M, Inoue M, et al. Characterization and Quality Control of Pharmaceutical Cocrystals. Chem Pharm Bull (Tokyo) 2016;64(10):1421-30. doi: 10.1248/cpb.c16-00233
4. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50(1):47-60. doi: 10.1016/S0939-6411(00)00076-X
5. Perlovich GL, Manin AN. Design of Pharmaceutical Cocrystals for Drug Solubility Improvement. Russ J Gen Chem 2014;84(2):407-14. doi: 10.1134/S107036321402042X
6. Bolla G, Nangia A. Pharmaceutical cocrystals: walking the talk. Chem Commun (Camb) 2016;52(54):8342-60. doi: 10.1039/C6CC02943D
7. Wohler F. Untersuchungen über des chinons. Annalen Chem Pharm 1844;51:145-63.
8. Desiraju GR. Crystal Engineering: The Design of Organic Solids. Amsterdam: Elsevier; 1989.
9. Desiraju GR. Supramolecular synthons in crystal engineering—A new organic synthesis. Angew Chem Int Ed Engl 1995;34(21):2311-27. doi: 10.1002/anie.199523111
10. Almarsson Ö, Zaworotko MJ. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? Chem Commun (Camb) 2004;0(17):1889-96. doi: 10.1039/B402150A
11. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, et al. Polymorphs, salts, and cocrystals: What’s in a name? Cryst Growth Des 2012;12(5):2147-52. doi: 10.1021/cg3002948
12. Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals. Center for Drug Evaluation and Research, United States Food and Drug Administration. https://www.fda.gov/downloads/Drugs/Guidances/UCM281764.pdf. Accessed on: 5 Jan 2018.
13. Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals. Revision-1, Center for Drug Evaluation and Research, United States Food and Drug Administration. http://www.fda.gov/Drugs/GuidanceCompliance/RegulatoryInformation/Guidances/UCM516813.pdf. Accessed on: 5 Jan 2018.
14. Qiao N, Li M, Schindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. Int J Pharm 2011;419(1-2):1-11. doi: 10.1016/j.ijpharm.2011.07.037
15. Desiraju GR. Chemistry beyond the molecule. Nature 2001;412(6845):397-400. doi: 10.1038/35086640
16. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Cryst Growth Des 2009;9(6):2950-67. doi: 10.1021/cg900129f
17. Duggirala NK, Perry ML, Almarsson O, Zaworotko MJ. Pharmaceutical cocrystals: along the path to
Recent Regulatory Updates on Cocrystals

Improved medicines. *Chem Commun (Camb)* 2016;52(4):640-55. doi: 10.1039/C5CC08216A

18. Kumar S, Nanda A. Pharmaceutical Cocrystals: An Overview. *Indian J Pharm Sci* 2017;79(6):858-71. doi: 10.4172/2271-545X.1000302

19. Cruz-Cabeza AJ. Acid-base crystalline complexes and the pH rule. *CrystEngComm* 2012;14(20):6362-5. doi: 10.1039/C2CE26055G

20. Laszlo F. Cambridge structural database analysis of molecular complementarity in cocrystals. *Cryst Growth Des* 2009;9(3):1436-43. doi: 10.1021/cg800861m

21. Abramov YA, Loschen C, Klamt A. Rational coformer or solvent selection for pharmaceutical cocrystallization or desolvolation. *J Pharm Sci* 2012;101(10):3687-97. doi: 10.1002/jps.23227

22. Mohammad MA, Alhalawe A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. *Int J Pharm* 2011;407(1-2):63-71. doi: 10.1016/j.ijpharm.2011.01.030

23. Musumeci D, Hunter CA, Prohens R, Scuderis S, McCabe JF. Virtual cocrystal screening. *Chem Sci* 2012;3(2):883-90. doi: 10.1039/C2SC00555J

24. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. *CrystEngComm* 2008;10(6):665-8. doi: 10.1039/B801713C

25. Berry DJ, Seaton CC, Clegg W, Harrington RW, Coles SJ, Horton PN, et al. Applying hot-stage microscopy to co-crystal screening: a study of nicotinamide with seven active pharmaceutical ingredients. *Cryst Growth Des* 2008;8(5):1697-712. doi: 10.1021/cg80035S

26. Ross SA, Lamprou DA, Dourounis D. Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies. *Chem Commun (Camb)* 2016;52(57):8772-86. doi: 10.1039/C6CC01289B

27. Malamatari M, Ross SA, Dourounis D, Velaga SP. Experimental cocrystal screening and solution based scale-up cocrystallization methods. *Adv Drug Deliv Rev* 2017;117:162-77. doi: 10.1016/j.addr.2017.08.006

28. Dourounis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. *Adv Drug Deliv Rev* 2017;117:178-95. doi: 10.1016/j.addr.2017.07.008

29. Karki S, Friscic T, Jones W, Motherwell WD. Screening for pharmaceutical cocrystal hydrates via neat and liquid-assisted grinding. *Mol Pharm* 2007;4(3):347-54. doi: 10.1021/mp0700054

30. Aber S, Dhumal R, Mahadik K, Paradkar A, York P. Ultrasound assisted cocrystallization from solution (USSSC) containing a non-congruently soluble cocrystal component pair: Caffeine/maleic acid. *Eur J Pharm Sci* 2010;41(5):597-602. doi: 10.1016/j.ejps.2010.08.012

31. Alhalawe A, Velaga P. Formation of cocrystals from stoichiometric solutions of incongruently saturating systems by spray drying. *Cryst Growth Des* 2010;10(8):3302-5. doi: 10.1021/cg100451q

32. Bavishi DD, Borkhataria CH. Spring and parachute: How cocrystals enhance solubility. *Prog Cryst Growth Charact Mater* 2016;62(3):1-8. doi: 10.1016/j.pcrysgrow.2016.07.001

33. Pindelska E, Sokal A, Kolodzijski W. Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques. *Adv Drug Deliv Rev* 2017;117:111-46. doi: 10.1016/j.addr.2017.09.014

34. Thipparaboina R, Kumar D, Chavan RB, Shastri NR. Multidrug co-crystals: towards the development of effective therapeutic hybrids. *Drug Discov Today* 2016;21(3):481-90. doi: 10.1016/j.drudis.2016.02.001

35. Bhatt PM, Azim Y, Thakur TS, Desiraju GR. Cocrystals of the anti-HIV drugs lamivudine and zidovudine. *Cryst Growth Des* 2009;9(2):951-7. doi: 10.1021/cg8007359

36. USPTO. United States Patent and Trademark Office. [10 Jan 2018]; Available from: http://www.uspto.gov

37. EPO. European Patent Office. [10 Jan 2018]; Available from: http://www.epo.org

38. Desiraju GR. Pharmaceutical salts and co-crystals: retrospect and prospects. In: Wouters J, Quéré L, editors. Pharmaceutical Salts and Co-crystals. Cambridge: RSC Publishing; 2011. PP. 1-8.

39. Trask AV. An overview of pharmaceutical cocrystals as intellectual property. *Mol Pharm* 2007;4(3):301-9. doi: 10.1021/mp070001z

40. Reflection paper on the use of cocrystals of active substances in medicinal products. Committee for Medicinal Products for Human Use. European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500189927.pdf . Accessed on: 5 Jan 2018.

41. Fala L. Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure. *Am Health Drug Benefits* 2015;8(6):330-4.

42. Harrison WT, Yathirajan HS, Bindya S, Anilkumar HG, Devaraju. Escitalopram oxalate: co-crystals of oxalate diions and oxalic acid molecules in the same crystal. *Acta Crystallogr C* 2007;63(Pt 2):o129-31. doi: 10.1107/S010827010605520X

43. Mascitti V, Thuma BA, Smith AC, Robinson RP, Brandt T, Kalgrutkar AS, et al. On the importance of synthetic organic chemistry in drug discovery: reflections on the discovery of anti diabetic agent ertugliflozin. *MedChemComm* 2013;4(1):101-11. doi: 10.1039/C2MD20163A

44. Pfizer.com. Press Release Pfizer. [10 Jan 2018]; Available from: https://www.pfizer.com/news/press-release/press-release-detail/fda-approves-sglt2-inhibitor-steglatro_ertugliflozin_and_fixed_dose_combination_steglujan_ertugliflozin_and_sitagliptin_for_adults_with_type_2_diabetes.

Advanced Pharmaceutical Bulletin, 2018, 8(3), 355-363 | 361
45. Poole RM, Dungo RT. Ipraglitiflozin: first global approval. *Drugs* 2014;74(5):611-7. doi: 10.1007/s40265-014-0204-x

46. Chavan RB, Thipparobaina R, Yadav B, Shastri NR. Continuous manufacturing of co-crystals: challenges and prospects. *Drug Deliv Transl Res* 2018;19:1-4. doi: 10.1007/s13346-018-0479-7

47. Devarakonda SN, Vyas K, Bommareddy SR, Padi PR, Raghupathy B. Inventors; Reddy's Laboratories Ltd, Reddy's Laboratories Inc, assignee. Aripiprazole co-crystals. United States patent application US 2009/12/278,022.

48. estve.es. [8 Jan 2018]; Available from: http://www.esteve.es/EsteveFront/es/en/psd/idi_rd_portfolio_E-58425.jsp.

49. clinicaltrials.gov. United States National Library of Medicine. [15 Feb 2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT03108482?cond=co-crystals&ranks=1.

50. clinicaltrialsregister.eu. EU Clinical Trials Register. [15 Feb 2018]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=E-58425.

51. freshpatents.com. Fresh Patents. [15 Feb 2018]; Available from: http://www.freshpatents.com/-dt20111020ptan201102572125.htm.

52. Amos JG, Indelicato JM, Pasini CE, Reutzel SM. Complexes of cephalosporins and carbacephalosporins with parabens. US Patent 6001996A. Eli Lilly and Co Ltd (GB); 1995.

53. Remenar J, MacPhee M, Peterson M, Morissette S, Almarsson O. Crystalline forms of conazoles and methods of making and using the same. US Patent 7446107. TransForm Pharmaceuticals Inc; 2002.

54. Sependa GJ, Storey R. AZD1152; a phosphate prodrug and maleic acid co-crystal. US Patent 7625910. Astra Zeneca AB.

55. Imamura M, Nakanishi K, Shiraki R, Onda K, Sasuga D, Yuda M. Cocrystal of C-glycose derivative and L-proline. US Patent 8097592. Astellas Pharma Inc/Kotobuki Pharmaceutical Co Ltd; 2006.

56. Hanna M, Shan N, Cheney ML, Weyna DR. In vivo studies of crystalline forms of meloxicam. US Patent 8124603. Grunenthal GmbH/Thar Pharmaceuticals; 2008.

57. Childs SL. Metronidazole cocrystals and imipramine cocrystals. US Patent 8163790. New Form Pharmaceuticals Inc; 2006.

58. Grisenti P, Argese M, Scrocchi R, Liviari A, Guazzi G. Crystalline form of tiotropium bromide with lactose. US Patent 20170044176 A1. Euticals Spa; 2014.

59. Tan J, Shytle RD. Ionic co-crystal of lithium, lisprom, for the treatment of fragile x syndrome. US Patent 20170224724 A1. University Of South Florida; 2016.

60. Albert E, Andres P, Bevill MJ, Smit J, Nelson J. Cocryystals of progesterone. US Patent 20170101433 A1. AMRI SSCI LLC; 2012.

61. Oliveira M, Peterson M. Mixed co-crystals and pharmaceutical compositions comprising the same. EU Patent 1755388B1. TransForm Pharmaceuticals, Inc.

62. Zhang Y, Connelly PR, Johnston S. Co-crystals and pharmaceutical compositions comprising the same. EU Patent 2185546B1. Vertex Pharmaceuticals, Inc; 2011.

63. Mascitti V, Collman BM. Dioxabicyclo[3.2.1.]octane-2,3,4-triol derivatives. EU Patent 2334687B1. Pfizer Inc.

64. Ingelheim Pharma GmbH & Co. Kg Boehringer, Betageri R, Bosanac T, Burke MJ, Harcken C, Kim S, et al. Glucocorticoid mimetics, methods of making them, pharmaceutical compositions, and uses thereof. EU Patent 2300472B1. Boehringer Ingelheim Intl. GmbH.

65. Connelly PR, Kadiyala I, Stavropolis K, Zhang Y, Johnston S, Bhisetti GR, et al. Co-crystals and pharmaceutical compositions comprising the same. EU Patent 2114924B1. Vertex Pharmaceuticals Inc; 2007.

66. Grunenberg A, Queuekberg KF, Reute C, Keil B, Gushurst KS, Still EJ. New co-crystal compound of rivaroxaban and malonic acid. EU Patent 2288606B1. Bayer Pharma Ag.

67. Almarsson Ö, BourgholiHM, Peterson M, Zaworotko MJ, Moulton B, Hornedo NR. Pharmaceutical co-crystal of celecoxib-nicotinamide. EU Patent 1608339B1. University of South Florida Johnson and Johnson Consumer Inc: University of Michigan; 2003.

68. Tesson N, Esther C. Cocrystals of lorcaserin. EU Patent 3210975 A1. ENANTIA SL; 2016.

69. Kumar R, Vasam NS, Makreddy SR, Murki V, Ganorkar R, Jose J, et al. Co-crystal of carfilzomib with maleic acid and process for the preparation of pure carfilzomib. EU Patent 3240575 A1. Dr. Reddy's Laboratories Ltd; 2014.

70. Kumar S, Kishore N, Vittal, Sivakumaran MS. Process for the preparation dl-proline co-crystal of dapaglitiflozin. WO Patent 2017191539A1. Aurobindo Pharma Limited; 2016.

71. Wennogle LP, Li P, Aret E. Novel co-crystals. WO Patent 2017172811 A1. Intracellular Therapies, Inc; 2016.

72. Tesson N, Gordo CE. Cocrystals of lorcaserin. WO Patent 2017144598 A1. Enantia, S.L.; 2016.

73. Kocherlakota C, Banda N. Novel co-crystal forms of agomelatine. WO Patent 2017115284 A1. Leitius Pharmaceuticals Pvt, Ltd; 2015.

74. Albrecht W, Geier J, Sebastian, Perez D. Coocrystals of ibritunib with carboxylic acids. WO Patent2016156127 A1. Ratiopharm Gmbh; 2015.

75. Smith AJ, Kim SH, Duggirala NK, Jin J, Wojtas L, Ehrhart J, et al. Improving lithium therapeutics by crystal engineering of novel ionic cocryystals. *Mol Pharm* 2013;10(12):4728-38. doi: 10.1021/mp400571a
Recent Regulatory Updates on Cocrystals

76. Ong TT, Kavuru P, Nguyen T, Cantwell R, Wojtas L, Zaworotko MJ. 2:1 Cocrystals of homochiral and achiral amino acid zwitterions with Li⁺ salts: Water-stable zeolitic and diamondoid metal-organic materials. *J Am Chem Soc* 2011;133(24):9224-7. doi: 10.1021/ja203002w

77. Kruthiventi A, Roy S, Goud R, Javed I, Nangia A, Reddy JS. Synergistic pharmaceutical cocrystals. WO Patent 2009136408A4. Institute Of Life Sciences, S.O.C., University Of Hyderabad.

78. Dandela R, Reddy JS, Viswanadha GS, Nagalapalli R, Solomon AK, Gaddamanugu G, et al. Novel cocrystals/molecular salts of mesalamine to be used as improved anti-inflammatory drug. WO Patent 2012090224A1. Nutracryst Therapeutics Private Limited; 2010.

79. Reddy JS, Dandela R, Viswanadha GS, Nagalapalli R, Solomon AK, Javed I, et al. Novel cocrystals/molecular salts of metformin with oleylethanolamide as an effective anti-diabetic + anti-obesity agent. WO Patent 2012090225A2. Nutracryst Therapeutics Private Limited; 2010.

80. Kruthiventi AK, Javed I, Jaggavarapu SR, Nagalapalli R, Viswanadha GS, Anand SK. Pharmaceutical co-crystals of quercetin. WO Patent 2010134085A1. Nutracryst Therapeutics Private Limited; 2009.

81. Kumar A, Nanda A. Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries. *Pharm Regul Aff* 2017;6:1-6. doi: 10.4172/2167-7689.1000185