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Exploring the Patent Landscape and Regulatory Prospective on Pharmaceutical Cocrystals

Ritu Rathi[1], Yukta Guggal[1], Twinkle[1], Varneet Sandhu[1] and Inderbir Singh[1*]

[1]*Chitkara College of Pharmacy, Chitkara University, Punjab, India*

[*]inderbir.singh@chitkara.edu.in (Corresponding Address)

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ABSTRACT

Background: Cocrystals are not new, they have sparked considerable interest among scientists and the pharmaceutical business in the last decade. Cocrystals are multiphase formations composed of at least two particles that are held together by noncovalent bonds. Cocrystal offers unmatched physio-engineered attributes (like stability, melting point, taste concealment, dissolvability, purity, bioavailability, etc.) without changing the pharmacological capabilities of the drug. Recently, as pharmaceutical cocrystal development has increased, we have given more attention to the absurd state of cocrystals.

Purpose: The purpose of the current review is to explore the patent perspective on pharmaceutical cocrystals. And to discuss the new regulations that came up from the U.S. Food and Drug Administration (USFDA) and European Medicines Agency (EMA).

Methods: In order to accomplish the said objectives, literature was surveyed from GOOGLE PATENTS, GOOGLE SCHOLAR, PUBMED, EBSCO, etc. type for search engines for a detailed overview of the patentability and regulatory status of pharmaceutical cocrystals.

Conclusions: The journey of pharmaceutical cocrystals is bit challenging and still going on. In addition, if attention is drawn on some challenging aspects such as scalability, reproducibility, herbal bioactives cocrystals and 3D printed cocrystals related preparation and stability challenges, it can prove to be a paradigm shift in drug discovery processes.

1. Introduction

Cocrystals are single-phase, multicomponent crystalline solids composed of two or more ionic/ molecular compounds in stoichiometric ratios which are neither solvates nor hydrates. It is one of the most unique approaches as it does not affect the pharmacological properties but improves several physicochemical properties such as solubility, melting point, bioavailability, stability, drug release, tablet ability, and permeability (Kumar *et al.*, 2022). In 1844, Friedrich Wohler for the first time reported cocrystals, which then began to be discovered until the 1900s (Bolla *et al.*, 2022 and Kavanagh *et al.*, 2019). The formation of cocrystals is based upon the intermolecular interactions and their effect on crystal packaging. The cocrystals are held together by non-covalent interactions such as hydrogen bonding, Vander Waals forces, and π-π interactions (Thompson *et al.*, 2021). Cocrystals have gained significant attention of scientists from industry and academics as they are well known for enhancing the physicochemical properties of drugs (Nascimento *et al.*, 2021, Samineni *et al.*, 2019, and Kumar *et al.*, 2018). Cocrystals are now very popular for improving the solubility and stability of poor aqueous soluble neutral compounds, which is the most important in the case of BCS Class II and IV drugs. Design strategies, synthesis procedures, cocrystal characteristics with an emphasis on their applications, and regulatory, strategic, and patentability considerations are discussed in this review.

Since crystallization is based upon the change in physical properties of the drug at the molecular level that means the physicochemical properties of the drug can be altered by using different cocrystallization techniques. A cocrystal is composed of an API (Active Pharmaceutical Ingredient) and coformer in stochiometric ratios. The properties of cocrystals are based on the API and coformer properties, the nature of molecular interactions between them, and the method utilized for crystallization (Chavan *et al.*, 2018 and Vemuri *et al.*, 2019). The coformer used for cocrystal preparation should be based upon its ability to form hydrogen bonds with the API, solubility in the solvent, and compatibility with the API. The development of cocrystals also depends upon the method of crystallization (Samue *et al.*, 2022 and Thayyil *et al.*, 2020). Cocrystals can be prepared using solvent-based techniques and solvent-free techniques. The solvent-based techniques are versatile and

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ready-to-use techniques for the preparation of cocrystals that offer advantages such as scalability, reproducibility, adaptability, and controllability. The various solvent-based techniques include slow evaporation, slurry conversion, vapor diffusion, homogenization, ultrasound, and granulation. All the methods include mixing of drug and coformer within in suitable solvent followed by different processing conditions and expected outcomes such as gentle grinding, and sonication (Rathi *et al.*, 2022). Whereas the solvent-free techniques are called the green techniques involving very little or no solvent for preparing cocrystals. These techniques dominate solvent-based techniques as are environmentally friendly techniques with no harmful waste production, the cocrystals obtained are of high purity as no traces of toxic solvent are present, and are highly scalable. The various solvent-free techniques involve Hot melt extrusion, matrix-assisted, polymer-assisted, and liquid-assisted grinding. Other than these several other miscellaneous techniques are also used for developing cocrystals such as microwave, laser, electrospray, and resonate acoustic mixing (Rathi & Singh, 2022). The various cocrystal preparation techniques along with their advantages and disadvantages are mentioned below in Table 1.

Table 1: Various methods of preparation of cocrystals with advantages and disadvantages. Copyright@ American Chemical Society (Rathi *et al.,* 2021)

Methods of Co-crystallization		**Advantage**	**Disadvantage**
Solvent-based techniques	Solvent evaporation	• Easy-to-use approach and equipment • Screening and laboratory scale efficacy	• Single compounds crystals formation • Environmental hazardous
	Slurry conversion	• Easy-to-use approach and equipment • Preventing the formation of single compound crystals • Screening and laboratory scale efficacy	• Environmentally hazardous (small amounts of solvent • Scale-up is difficult
	Vapor diffusion	• Requires less energy as compared to mechano-chemical methods	• Dangerous to the environment (organic solvents)
	High pressure homogenization (HPH)	• Single step process • Scalability is simple.	• Harmful for the environment
	High shear granulation	• Prevents production of solvates	• Environmental hazardous
	Ultra-sound assisted	• Granulation with high shear	• Makes downstream processing easier • Process is complex • Not suitable for thermally labile drugs • Formation of solvates • A small number of studies
Solvent-free techniques	Neat grinding	• Green technique • Avoid formation of solvates • Polymorphic separation is possible	• Scale-up is difficult • Efficiency problems (mainly in manual grinding) • Time consuming
	Liquid assisted grinding	• Control of co-crystal characteristics and increased efficiency (mainly compared to neat grinding) • Rapid processing	• Dangerous to the environment (small amounts of solvent) • Formation of solvates • Difficult to scale up
	Hot melt extrusion	• Green method • Single step process • Continuous process • Scalable • High quality co-crystals • No solvates formed	• Not suitable for thermally labile drugs • Complicated technique (parameters equilibrium must be found)
	Matrix assisted	• Green method • Scalable • Easy Co-crystal synthesis and formulation Avoids the development of solvates	• Number of studies are limited
	Polymer assisted grinding	Prevents the production of solvates One-step procedure (only if polymers are biocompatible)	• Contaminants (if polymers are not biocompatible)

Miscellaneous techniques	Microwave assisted	• The green method (without solvents) • Avoids the production of solvates • Do not utilize shear forces, which are commonly used in solvent-free techniques.	• Limited number of studies
	Freeze drying	• Single step process • Continuous process • Easily scalable	• Environmental hazardous
	Electro spray	• Efficacy in screening • Single step • High purity co-crystals • High yield	• Use of organic solvents (low quantities)
	Laser Irradiation	• Control of the geometry of laser spots • Controlled energy deposition	• Expensive • High maintenance
	Resonant Acoustic Mixing	• Minor damage occurs to sample particulates, with no blades or impellers being used in the process • Diverse container compatibility and fast processing time.	• Limited number of studies

Once the cocrystal has been developed using suitable co-former and crystallization techniques, the next step is to characterize/evaluate the cocrystals for their morphology, drug content, and different physicochemical properties (Yadav *et al*. 2019 and Kshrisagar *et al*. 2022). Cocrystals can be characterized using different instrumental and non-instrumental techniques. The techniques include single crystal X-ray Diffraction (SCXRD) which provides the 3D structure of the cocrystal, power X-ray diffraction (PXRD) which tells about the phase and presence of any impurities, Fourier Transmission Infrared (FTIR) Spectroscopy, it provides information different functional groups involved and changes hydrogen bonding in the cocrystal, Raman spectroscopy is similar to FTIR but is more sensitive and provide information about molecular interactions (Gaggero *et al*., 2020 and Pawar *et al*., 2021). To study the thermal properties the DSC (Differential Scanning Calorimetry) and TGA (Thermogravimetric Analysis) were studied providing melting point and thermal stability respectively (Thakor *et al.,* 2020 and O' Sullivan *et al*., 2022). The cocrystals were morphologically evaluated using SEM (Scanning Electron Microscopy) for their surface and particle size (Fang *et al*., 2019 and Xiao *et al*., 2023). The various instrumental techniques for characterizing cocrystals along with their working principle are mentioned below in Table 2.

Table 2: Various methods along with their working principle for characterization of cocrystals

Techniques	**Working Principle**	**Uses**
DSC	Measurement of temperature difference between sample and reference material which is evolved or absorbed by the sample	For studying the thermal properties of the compound (melting point, glass transition temperature)
TGA	The change in weight of the sample is recorded as a function of time or temperature	Measure thermally induced weight loss of a material
XRD	Based on the constructive interference of monochromatic X-rays and extrudates	To detect the crystalline properties of the compound
IR	Based upon the emission of infrared light and reflection for detection	Involvement of different functional groups
NMR	Based on the spin of atomic nuclei	To probe the crystallinity of materials
SEM	It is based on the formation of an image using electrons instead of light	Surface morphology study

2. Regulatory Prospective of Cocrystals

When any pharmaceutical cocrystal of favorable outcomes is been created, the subsequent stage might acquire administrative endorsement so it very well may lead the way to advertising. Notwithstanding, the absence of clear administrative rules is a significant issue to handle. Throughout the most recent tenner, cocrystal improvement has seen huge development, there were even a couple of licenses allowed for cocrystals. For a development, to be patentable, innovation should satisfy the 3 conditions, for example, oddity, no conspicuousness, and utility/ convenience (Kumar *et al.*, 2018).

The United States of America (USA) and the European Union (EU) are the largest markets in the world, still have not developed many regulatory guidelines for pharmaceutical cocrystals because they are a fairly fresh API form. To incorporate pharmaceutical cocrystals in medicines meant for the US and the EU, various regulatory standards must be met (Gadade *et al.*, 2016). To determine whether pharmaceutical cocrystals are acceptable for registration in both the USA and the EU, as well as whether the features of this API form correspond with the regulations of both territories, the regulatory guidance documents issued by the US Food and Drug Administration and the European Medicines Agency will be reviewed and discussed.

As per the US FDA (US Food & Drug Administration, 2018), there are two reasons why it is important to know specifically if an API is a salt or a cocrystal. From a regulatory perspective, a different salt of a drug is considered a different API whereas a new cocrystal is not. That means that seeking approval for a drug product containing a salt of an approved API requires an Abbreviated New Drug Application [ANDA 505(b)(2)], which requires an Agency review of clinical data to assess safety and effectiveness. However, a 505(b)(2) application can rely on clinical data found in the literature or generated by the original New Drug Application filer. On the other hand, to seek approval for a drug product containing a cocrystal of an approved API only an ANDA 505(j) application needs to be used. That application does not require FDA review of clinical data (Ringle *et al.*, 2018).

Cocrystals can be thought of as a particular kind of hydrate and solvent from a regulatory point of view, in which another component, also known as the co-former, is usually non-volatile and not a form of solvent (including water). The following points should be supported by the relevant data submitted through applicants for both the NDAs/ ANDAs that contain or appear to have a cocrystal form:

- Confirmed that an API as well as co-formers that are there in the unit cell, provide affirmation.
- If the both, co-former and the API have their ionizable functional groups, then it may be assumed that they are present in the cocrystal and that their reactions are non-ionic. To help you decide, think about the following:

If the pKa of the API as well as its co-former are greater than 1 (pKa (acid) - pKa (the conjugate acid of base)), significant proton transfer will occur, which will lead to ionization and possibly the production of the salt rather than the cocrystal. In contrast, it is going to be less than considerable proton transfer if both the API with co-former possess ΔpKa (the pKa (the conjugate acid of base) that is - pKa (acid)) < 1. If this condition is met, the API co-former object needs to be categorized as a cocrystal. If it is determined that any pharmaceutical solid's categorization as either a salt or a cocrystal does not influence its relative pKa values, then utilize spectroscopic equipment and other orthogonal ways to provide evidence. Ensuring that the API widely separates from its cocrystal form before getting to the pharmacologically active location. Since the interaction between the API and its co-former is comparable to that between the API and solvents in solvates, an in vitro assessment based on dissolution is usually deemed sufficient to show that the API separates from its co-former before attaining the site of its pharmacological action. Any cocrystal that meets the aforementioned requirements and has a pharmaceutically approved co-former is categorized as a pharmacological cocrystal and undergoes regulation similarly to an API polymorph. In particular, it isn't considered a novel API. Drug products intended to incorporate novel cocrystals are considered from a regulatory standpoint as being comparable to novel polymorphs of active pharmaceutical ingredients (APIs). A cocrystal that contains more than one API (either with or without supplementary inactive co-formers) is a fixed-dose product rather than a new single API. A person may continue to use a component that the Agency has already determined to be part of a cocrystal at this point. The cocrystal should go through sufficient characterization and release testing for the confirmation of their potency, identity, purity, and quality of the API(s). (FDA Guidance Document).

As discussed above seeking the approval of a drug containing cocrystal ANDA 505(j) is required, for which the Drug Price Competition and Patent Term Restoration Act was developed. This act came into existence in 1984, also known as the Hatch-Waxman Act. This act mainly focuses on the generic drugs approval pathways, by which any generics can be launched in the market through the Abbreviated New Drug Application (ANDA) under 505(j) of the Federal Food, Drug, and Cosmetics Act. This act ensures the fast entry of generic drugs to the market by seeking FDA Approval. ANDA is required for filing to make sure that the generics are equivalent to the innovator drugs in all the terms including, the pharmaceutical equivalence, bio-equivalence, and the cGMP considerations. There are four certifications by which application filing is done for generics (as per patents filed for the reference drugs), shown in Figure 1.

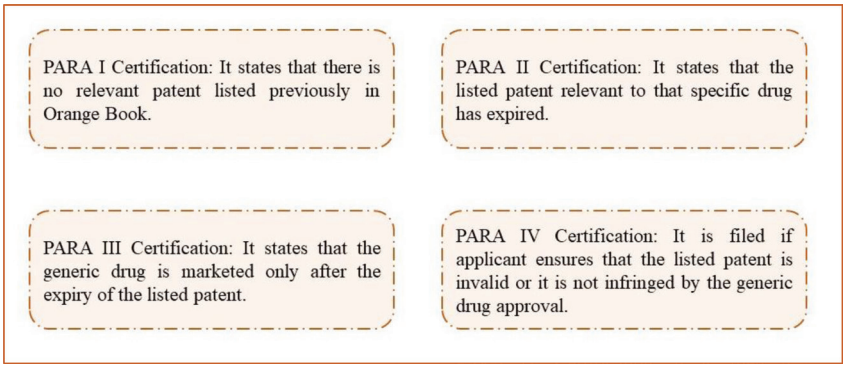

Figure 1: Different certifications for filing of generics

Now, if discussing about the regulatory body of Europe; The European Medicines Agency, the documentation of cocrystals can be done based on similarities between the cocrystals and the salts (European Drug Administration, 2018). Therefore, the guidelines given for the documentation of the salts are meant to be followed for the cocrystals. As the requirement demands, Quality-related data should be submitted in the dossier's part 2. C, including details about the drug substance's production, characterization, control, reference standards, container-closure mechanism, and stability. The pharmacological acceptability of co-formers is crucial, with common substances considered reagents in ICH Q11. More complicated or unique co-formers should be supplied, along with safety data. Consult the European Medicines Agency or national authorities for scientific advice. Cocrystal creation should be demonstrated using appropriate analytical techniques to avoid a physical mixture of crystalline compounds. If discussing the approval procedures for EMA; they are the Decentralized Procedure and the Mutual Recognition Procedure. The first assessment can be performed by the decentralized procedure and mutual recognition in European member states. When a drug product did not receive the Market authorization at the time of application, in that case Decentralized Procedure is preferred instead of a Mutual Recognition Procedure. 2004/27/EC directive gives the introduction about Decentralized Procedure. Several applications vary according to the nature of the active substance of its pharmaceutical product. For new active substances (NAS) a "full application" is submitted. Companies have to submit a dossier for approval which includes the information related to clinical trials, pharmaceutical tests, and preclinical tests. Cocrystals, hydrates, solvates, and salts cannot be considered new active substances unless they are demonstrated to be different concerning efficacy and/or safety concerning all routes of administration. On receiving a marketing authorization for a new active substance an assessment is to be done by the competent authorities to ensure that the claimed active substance is new indeed. Polymorphic forms of a single entity active substance, or salts, cocrystals, hydrates, or solvates, will also not be considered NASs in themselves as they come under the abridge application. The application for drugs containing existing active substances is described as "abridged applications". Abridged applications Prevent to performance of unnecessary tests and trials of similar authorized products. Abridged applications can be submitted for various products, the products are listed below in Figure 2.

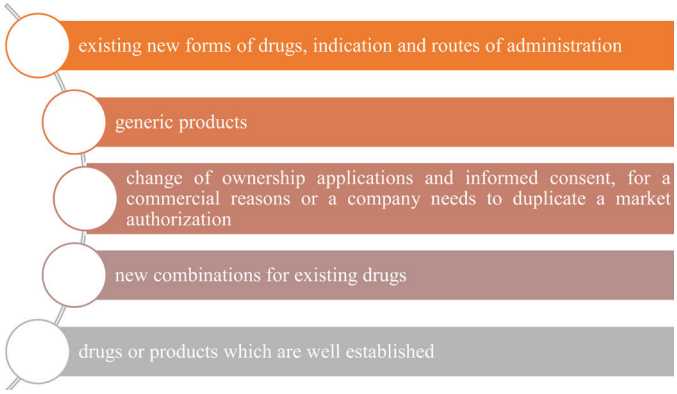

Figure 2: List of products requiring abridged application submission

Cocrystals and abridged applications: Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC 13(2)(b) define what can be considered as the same active substance in the context of accepting an abridged application. Cocrystal hydrates and solvates are weakly bonded and these interactions break down on dissolution. This situation is the same with salts. Concerning all routes of administration there is possibly no difference in the safety and efficacy of different forms of a drug substance. Because, when it gets dissolved in the stomach and intestine it leads to the release of the same substance independent of its form that was taken in. This assumption can be verified by bioequivalence. So, according to (Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC) If there is no difference in the safety and efficacy of cocrystals, hydrates, and solvates they can be considered eligible for generic applications in the same way as salts.

a. Acceptance of ASMF for cocrystals: The active substance quality documents known as active substance master files submitted directly to a regulatory authority. The acceptance of this document relies on the directive 2001/82/EC or 2001/83/EC.
b. Acceptance of cocrystals containing more than one therapeutic moiety

A pharmaceutical product containing an active substance which can be more than one in a solid state. If the solid-state form is a cocrystal and the cocrystals are physical materials for manufacturing of a pharmaceutical product. Despite being physical products the characterized from a pharmaceutical and chemical perspective are also required. The cocrystal's stoichiometry does not have to be confined to equimolar levels. The dose ratio of the separate active chemicals must be carefully justified because it is determined and limited by the relative stoichiometry within the cocrystal. The effect of cocrystallization on the bioavailability of individual active compounds should be discussed and this medicinal product of solid state (cocrystal) must apply for the fixed dose combination. The similarities and differences in FDA and EMA are represented below in Figure 3.

Table 3: FDA and EMA regulatory approval of pharmaceutical cocrystals

Regulatory considerations	Food and Drug Administration guidance	European Medicines Agency
Category of regulation	Polymorph of the active pharmaceutical ingredient	Active pharmaceutical ingredient
Composed of	An active pharmaceutical ingredient and a food or drug grade coformer	Active pharmaceutical ingredient and coformer in fixed stoichiometric ratio
Crystallographic interaction	Non-ionic or non-covalent interactions	Non- ionic or non-covalent interactions
Registration of novel chemical entity or active substance	No	Possible if proven a difference in the efficacy or the safety
Similarity with active pharmaceutical ingredient	Similar	Similar unless proven to have distinct efficacy/ safety
Cocrystal and salt	Variation in the regulatory pathway and the interaction	Regulation relies on the safety or efficacy
US- DMF (Drug master files) / EMA-ASMF (Active substance master file)	No	Can be filed for new active substance registration
The role of a coformer	Excipient	Reagent
Expected manufacturing facility	Drug product facilities	API manufacturing facilities

3. Patents on Cocrystals

Pharmaceutical cocrystals observed huge development and many exploration papers and licenses have been documented in the world till date, several cocrystallization and multi-drug cocrystallization licenses have been granted. A few of the most recent drug cocrystal definitions and a list of approved drugs cocrystal licenses in the United States, Europe, and other countries are listed below in table 3-5.

3.1. Patents in the USA

Table 4: List of cocrystal patents in the USA

PUBLICATION NO.	DATE	ASSIGNEE	TITLE	REFERENCES
US20070100143A1	2007-05-03	Hetero Drugs Limited	Crystalline alfuzosin base	Reddy *et al.,* 2007
US20110014282A1	2011-01-20	De Vasconcelos Teofilo Cardoso	Pharmaceutical composition for poorly soluble drugs	Vasconcelos *et al.*, 2011
US20110275682A1	2011-11-10	Bionevia Pharmaceuticals, Inc	Novel choline cocrystal of epalrestat	Kalofonos *et al.,* 2011
US20140004051A1	2014-01-02	University Of Iowa Research Foundation	Cocrystals and salts of contrast agents and imaging	MacGillivray *et al.*, 2014
US10280124B2	2019-05-07	Cpi Innovation Services Limited	Making active crystalline materials methods	Ahmad *et al.*, 2019
US10292951B2	2019-05-21	First Wave Bio, Inc.	Treatment methods and formulations for illnesses involving an inappropriate inflammatory response	Glick *et al.*, 2019
US10508096B2	2019-12-17	R.J. Reynolds Tobacco Company	Cocrystals, salt cocrystal complexes, and nicotine salts	Gary M. Dull *et al.*, 2019.
WO2021/138610 A1	2021-07-08	Purysis LLC	Cocrystals of cannabinoids	Mkrtchyan *et al.*, 2021
US 2022/0363661 A1	2022-11-17	Servier Pharmaceuticals LLC	Cocrystals, pharmaceutical compositions thereof, and methods of treatment involving the same	S. Lane *et al.*, 2022
WO/2021/260519	2021-12-30	SAVOI, Guilherme	Cocrystals derivatives of apixaban	Savio *et al.*, 2021
WO/2021/022103	2021-02-04	THE REGENTS OF THE UNIVERSITY OF MICHIGAN	Cocrystals of posaconazole, methods of making and using the same	Hornedo *et al.*, 2021
US 8,920,559 B2	2011-10-13	Aptuit (West Lafayette), LLC, West Lafayette, IN (US)	Screening for solid forms by ultrasound crystallization and crystallization using ultrasound	Childs *et al.*, 2014
US011608324B2	2023-03-21	The children's hospital of Philadelphia	Solid forms of fasoracetam.	Lessons *et al.*, 2023
US 2014/0235595 A1	2014-08-21	Aptuit, Inc., West Lafayette, IN (US)	Cocrystals of progesterone	ALBERT *et al.*, 2014

3.2. Patents in Europe

Table 5: List of cocrystal patents in Europe

PUBLICATION NUMBER	DATE	ASSIGNEE	TITLE	REFERENCE
EP2937346A1	2015-10-28	F.I.S.- Fabbrica Italiana Sintetici S.p.a	Cocrystals of lapatinib	Tesson *et al.*, 2015
EP2056798A2	2009-05-13	Amgen, Inc	Sorbic acid analog cocrystals	Annete bak *et al.*, 2009

EP2167043A4	2013-05-01	Univ South Florida	Nutraceutical cocrystal compositions	Zaworotko *et al.*, 2013
EP2177215A1	2010-04-21	Laboratorios Del. Dr. Esteve, S.A.	Cocrystals of tramadol and NSAIDs	Buschmann, *et al.*, 2011
EP2340818A1	2011-07-06	Laboratories Del. Dr. Esteve, S.A.	Cocrystals of venlafaxine and celecoxib	Salaman *et al.*, 2011
EP2688575B1	2016-03-23	University of South Florida	Lithium compositions	ZAWOROTKO *et al.*, 2016
WO/2017/211733	2017-12-14	Enantia, S.L.	Chiral resolution of an intermediate of suvorexant and cocrystals	Comely *et al.*, 2017
EP 3 339 292 A1	2018-06-27	Zaklady Farmaceutyczne Polpharma SA 83-200 Starogard Gdanski (PL)	Cocrystals of apremilast	ORACZ *et al.*, 2018
Wo 2020/089424 A1	2019-10-31	Parc cientific de barcelona	Solid composition of co-crystals of cannabinoids	Tesson *et al.*, 2020
EP 3 674 287 A1	2020-07-01	Zaklady Farmaceutyczne "Polpharma" S. A	cocrystals of (r)-baclofen	Tesson *et al.*, 2020
Wo 2019/162429	2019-08-29	Center for intelligent research in crystal engineering	Cocrystals of ubiquinone and compositions comprising them	lopen *et al.*, 2019.
WO2017/144598 A1	2017-08-31	Enantia, S.L. 08028 Barcelona (ES)	Cocrystals of lorcaserin	Nicolas *et al.*, 2017

3.3. Some International Patents

Table 6: List of cocrystal patents in other countries

PUBLICATION NUMBER	DATE	ASSIGNEE	TITLE	REFERENCE
CN102952138B	2016-07-06	Shanghai Tehua Pharmaceutical Technology Co., Ltd.	The salt of a kind of pyrazole pyrimidinone compound, polymorph and pharmaceutical composition, preparation method, and application	Shanghai tehugoogi le ek a pharmaceutical technology co., ltd. *et al.*, 2016
NZ710780A	2017-02-24	Salix Pharmaceuticals Ltd	New forms of rifaximin and uses thereof	Parent *et al.*, 2017
TW201131192A	2011-09-16	Univ Nat Central	cocrystal compound of optical devices	Tu Lee *et al.*, 2011
AU2013201664B2	2015-08-13	Theaprin Pharmaceuticals Inc.	Intravenous formulation including water-soluble acetylsalicylic acid and theanine cocrystals.	Brittain *et al.*, 2015
Wo 2017/111179 A1	2017-06-29	Takeda Pharmaceutical Company Limited	Cocrystal, production method thereof, and medicament containing cocrystals	Kimoto *et al.*, 2017
CN108495563B	2022-04-26	RJ Reynolds Tobacco Co	Nicotine salts, co-crystals and salt co-crystal complexes	Dahl *et al.*, 2022
JP2007516259A	2007-06-21	Med Crystal Forms, LLC	Method for preparing mixed phase cocrystal with activator	Goldman *et al.*, 2007

4. Conclusion and Future Perspectives

Cocrystallization is a suitable approach for redesigning a drug's physicochemical properties and preserving the API's pharmacological properties. However, the assessment of some important factors is to be considered. One of the major challenges in the development of drug cocrystals is ensuring API coformer compatibility. The large-scale production of co-crystals encountering process, equipment, and material parameters are to be considered for developing robust scalable methods for the continuous production of cocrystals. Other than the scale-up of cocrystals, the safety, efficacy, toxicity, and stability of co-crystals should also be considered. Since some of the literature is already been reported for cocrystal preparation by 3D printing but there is a need of critical process and equipment parameters optimization for the rapid and continuous production of cocrystals. Another research area is the preparation of herbal cocrystals, the selection of herbal bioactive, and the suitable coformer. Moreover, a standardized regulatory guideline for their approval.

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Authorship contribution

Conceived and designed the experiments: Inderbir Singh. Analyzed the data: Inderbir Singh and Ritu Rathi. Wrote the manuscript: Yukta Guggal and Twinkle. Visualization: Inderbir Singh. Editing of the Manuscript: Varneet Sandhu and Yukta Guggal. Critically reviewed the article: Inderbir Singh and Ritu Rathi. Supervision: Inderbir Singh.

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The authors declare no conflict of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

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Chitkara University, Saraswati Kendra, SCO 160-161, Sector 9-C, Chandigarh, 160009, India

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