Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2023, 12(4):1-4
https://doi.org/10.51847/eGq6tbgNvd

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Pharmaceutical Cocrystals a Patentable Composition - A Review

Karthikeyan Ramadoss[1]*, Haema Ganapathi[1], Vijayan Venugopal[1], Sakthiganapathi Meenatchi Sundaram[1], Shanmuganathan Seetharaman[1], Velmurugan Vadivel[2]

[1]School of Pharmacy, Sri Balaji Vidyapeeth, SBV Campus, Pillaiyarkuppam, Puducherry, India.
[2]SRM College of Pharmacy, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, Kattankulathur – 603 203, India.

***Email:** professorrkn@gmail.com*

ABSTRACT

The major topic of this review study involves the connection between particular scientific, legal, and regulatory elements of pharmaceutical crystal forms. By referring to current scientific advancements in this area, the article provides an examination of pharmaceutical co-crystals as patentable inventions. The following few potential business benefits of pharmaceutical co-crystals and the other recent court rulings concerning important problems are compiled. The regulatory status of co-crystals has become a major concern recently with the rise of pharmaceutical co-crystals. The situation has grown even more problematic as a result of the new regulations from the European Medicines Agency (EMA) and the United States Food and Drug Administration (USFDA), as there are vastly divergent viewpoints. The essay offers a perspective on the potential effects of co-crystallization on the landscape of pharmaceutical intellectual property. Another point that has been considered is whether co-crystals qualify for patent protection in accordance with the literature and standards on pharmaceutically approved co-crystals.

Key words: *Pharmaceutical cocrystal, Synthons, Intellectual property, Patent law*

INTRODUCTION

Certain crystals are known to cohabit as supramolecular synthons. Since then, there have been significant changes. In 1773, the first cocrystal of urea with NaCl was found [1]. The first cocrystal of benzoquinone and hydroquinone (also known as quinhydrone) with a 1:1 ratio was produced in 1844. Quinhydrone electrodes were later developed to gauge the amount of hydrogen ions present in an acidic solution. Few investigations on the characteristics of the cocrystals were published as the interest in comprehending the chemistry of co-crystallization somehow faded. The possibility of using co-crystallization to produce pharmaceutical cocrystals was brought to light when the FDA authorized practical supramolecular synthons including Lexapro (2002), Calcit for infantile apnea (1993), and Depakote for epilepsy.

Supramolecular cocrystals have found success and acceptance in the fields of medicine, materials science, and pharmaceuticals. As a result, the pharmaceutical industry is now looking to patent these new supramolecular crystals to use in the field of disease management without first obtaining FDA approval. The pharmaceutical sector started concentrating on producing more cocrystals of APIs and other synthons for the patient care product market at that time, instead of limiting to only polymorphs, metabolites, prodrugs, isomers, and so on.

Co-crystals as inventions

A pharmaceutical cocrystal must meet the same criteria for novelty, utility, and non-obviousness in order to be granted a patent, just like the claimed subject matter of any patent application [2-4]. A cocrystal is a separate solid-state substance that often has an unusual and unexpected structure and physical property profile. The term "crystalline molecular complexes" has a wide meaning that includes hydrates and solvates, which are medicinal crystal forms with a track record of patentability. Likewise, cocrystals including complexes of the API and other counter compounds need to be considered patentable innovations as well. The significance of current research into this new class of pharmaceutical crystal forms is highlighted by evaluating certain characteristics that render cocrystals typically patentable.

Novelty

Co-crystallization offers an alternative to pharmaceutical salt production for solid-state alterations of APIs; in this way, it performs a similar purpose [5]. Co-crystals should satisfy the novelty criteria in the same way that salts do because they are innovative and distinctive solid-state structures.

The importance of pharmaceutical cocrystal patents

As with patents on new molecular entities, patents on pharmaceutical cocrystals may be important to the pharmaceutical industry in several key respects.

Commercial advantages

A research organization usually submits a patent application covering an API's chemical structure as soon as it becomes clear that the API has therapeutic potential in order to thwart a competing organization from filing on the same molecule independently. As a result, the primary justification for a patent's protection of a marketed pharmaceutical product typically stems from statements regarding an API's chemical makeup. However, in certain cases, further patent protection might be obtained by patenting fresh, solid variants of the API that were discovered as it was being created.

Position in the United States of America and the European union

In the US and Europe, numerous patents for cocrystals suitable for use in pharmaceuticals have been approved. Consider the co-crystal of parabens and (carba)cephalosporins (US 60001996), Itraconazole cocrystals with a carboxylic acid (US 7446107), AZD1152 cocrystals with a maleic acid and phosphate prodrug (US 7625910), and so forth [6]. Cocrystals are the subject of several European patents, such as (EP1755388B1) for mixed modafinil cocrystals, (EP2185546B1) for cocrystals and telaprevir (VX-950), and (EP2334687B1) for SGLT-2 inhibitors, l-proline, and pyroglutamic acid. Among others, celecoxib with nicotinamide cocrystals (EP1608339B1). Similarly, numerous patent applications are pending for Drug-Drug Cocrystals. Quercetin-metformin (antioxidant and anti-diabetic); Metformin-oleoyl ethanolamide (antidiabetic and anti-obesity); and Mesalamine with alpha-amino acids, flavones, and nutraceuticals (anti-inflammatory) are some examples [7-9].

Co-crystal patentability: Indian perspective

A novel chemical entity, solid state, or formulation, as well as manufacturing procedures (for example, a chemical synthesis pathway), are typical subject matters that are eligible for pharmaceutical patents in India. Even techniques of use or specific second medical indications are permitted in some patent jurisdictions. A real invention may be patented under Indian patent law [10]. The evergreening of a patent is not supported by the Indian patent system. Therefore, under Section 3(d) of the Patents Act, neither the novel use nor the new form of a known substance may be considered patentable. To the extent that their properties are not dramatically different, they include salts, esters, ethers, polymorphs, metabolites, pure forms, particle sizes, isomers, mixes of isomers, complexes, combinations, and other derivatives of recognized substances. When we assess how crystallization occurs, we can see that cocrystals are entirely novel compounds that readily satisfy the originality test outlined in Section 2(1)(j). Because it is unclear how to successfully obtain cocrystals in practice, the obviousness barrier is not a concern. Even with the use of conventional co-crystallization techniques, getting cocrystals suitable for pharmaceutical applications is a time-consuming and difficult operation. Cocrystals, in contrast to other types of solid forms, have distinct scientific benefits that make them patentable and give them access to regulatory advantages, new intellectual property opportunities, and intellectual property problems.

Meeting the criteria for patentability

Whether the selected molecules will link together to form a cocrystal within a crystal lattice as opposed to crystallizing separately as the physical mixture itself is the major query highlighted by the patent application for cocrystals. If such occurs, an objection would be a difficult hurdle to clear under Section 3(d) [11]. In certain circumstances, the person seeking approval may investigate any pharmacological synergy of the combination. Whether cocrystals meet the criteria for patent eligibility or not. Much will rely on how the applicant responds to each objection the examiner raises. However, the petitioner needs to provide evidence for that.

1. Co-crystallization of a particular pair or more of molecular components in a specific cocrystal structure.
2. Primary intermolecular interactions, such as hydrogen-bond motifs,
3. Overall packing arrangements, and are all formed.

Observing forward

Chemical informatics may aid in the search for pharmaceutically acceptable cocrystals by exploring polymorphs, hydrates, salts, and amorphous solids. It is worth noting that several cocrystals that are suitable for use in medicine have received approval from drug regulatory agencies. When two physiologically active molecules combine, drug-drug cocrystals can occur. A cocrystal between the antiviral drugs zidovudine and lamivudine, both of which are efficacious against HIVF, has been discovered, for example. Notable accomplishments include the filing of a patent application (WO Patent 2009136408A4) for medicinal cocrystals by Indian researchers from the Institute of Life Sciences at the University of Hyderabad [12-14]. The goal of creating multi-drug cocrystals is to create acceptable drug combinations that can be used to treat multi-drug resistance, find therapeutic pairings that work well together or create brand-new medications.

CONCLUSION

The Indian examiner at the Indian Patent Office was not averse to granting a patent on cocrystals. First-generation co-crystals satisfy the requirements for a patent to be granted. The new medication cocrystals will affect the status of medical engineering as it stands in the pharmaceutical sector. Drug-drug co-crystallization also gives generic producers a chance to create brand-new, pharmaceutically acceptable crystals to obtain patent protection for already marketed compounds or to avoid being subject to existing patents on similar molecules. To acquire a patent on pharmaceutically approved cocrystals, expert guidance would be helpful.

ACKNOWLEDGMENTS : The authors are thankful to the management of Sri Balaji Vidyapeeth for helping by providing the facility to complete this review work.

CONFLICT OF INTEREST : None

FINANCIAL SUPPORT : None

ETHICS STATEMENT : None

REFERENCES

1. 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. 2004;35(17):1889-96.
2. Al-Dulaimi AF, Al-kotaji M, Abachi FT. Co-crystals for improving solubility and bioavailability of pharmaceutical products. Egypt J Chem. 2022;65(1):81-9.
3. Vippagunta SR, Brittain HG, Grant DJ. Crystalline solids. Adv Drug Deliv Rev. 2001;48(1):3-26.
4. Zheng L, Zhu B, Wu Z, Fang X, Hong M, Liu G, et al. Strategy for efficient discovery of cocrystals via a network-based recommendation model. Cryst Growth Des. 2020;20(10):6820-30.
5. Guillory JK. Handbook of Pharmaceutical Salts: Properties, Selection, and Use Edited by P. Heinrich Stahl and Camile G. Wermuth. VHCA, Verlag Helvetica Chimica Acta, Zürich, Switzerland, and Wiley-VCH, Weinheim, Germany. 2002. ISBN 3-906390-26-8.
6. MacFhionnghaile P, Crowley CM, McArdle P, Erxleben A. Spontaneous solid-state cocrystallization of caffeine and urea. Cryst Growth Des. 2020;20(2):736-45.

7. Ramya MG, Krishna KC. Pharmaceutical Co-Crystals: An Overview on Synthesis and Regulatory Aspects. J Drug Deliv Ther. 2019;9(4):623-8.
8. Villani FJ, Wong JK. inventor, Merck Sharp and Dohme Corp, assignee, United States, U.S. Patent No. 4659716 A (Apr 21, 1987-2007).
9. Vioglio PC, Chierotti MR, Gobetto R. Pharmaceutical aspects of salt and cocrystal forms of APIs and characterization challenges. Adv Drug Deliv Rev. 2017;117:86-110.
10. Tandon R, Tandon N, Thapar RK. Patenting of polymorphs. Pharm Pat Anal. 2018;7(2):59-63.
11. Liu F, Jiang FB, Li YT, Liu RM, Wu ZY, Yan CW. Cocrystallization with syringic acid presents a new opportunity for effectively reducing the hepatotoxicity of isoniazid. Drug Dev Ind Pharm. 2020;46(6):988-95.
12. Bruni G, Maggi L, Mustarelli P, Sakaj M, Friuli V, Ferrara C, et al. Enhancing the pharmaceutical behavior of nateglinide by cocrystallization: Physicochemical assessment of cocrystal formation and informed use of differential scanning calorimetry for its quantitative characterization. J Pharm Sci. 2019;108(4):1529-39.
13. Luo Y, Chen S, Zhou J, Chen J, Tian L, Gao W, et al. Luteolin cocrystals: Characterization, evaluation of solubility, oral bioavailability and theoretical calculation. J Drug Deliv Sci Technol. 2019;50:248-54.
14. Germann LS, Arhangelskis M, Etter M, Dinnebier RE, Friščić T. Challenging the Ostwald rule of stages in mechanochemical cocrystallisation. Chem Sci. 2020;11(37):10092-100.