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MINI REVIEW

From Crystallography to Crystal Engineering of Pharmaceutical Cocrystals

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ABSTRACT

Crystal engineering has emerged as a method to obtain pharmaceutical cocrystals, a solid form of an existing active pharmaceutical ingredient, which can lead to altered physico-chemical properties without covalent modification in the existing APIs. The overall developed in obtaining pharmaceutical cocrystals has come up by the growth in viability of existing APIs as time and cost spent on obtaining new chemical entity is tremendous and acceptance of these as a solid form by both United States Food and Drug Administration and European Medicines Agency. Another aspect and challenge of immense importance is to obtain API-API cocrystals, which can be formulated in fixed dosages in pharmaceutical cocrystals. A few examples of API-API cocrystals existing in the market and potential candidates in different stages of their clinical trials are highlighted in this mini review.

KEYWORDS

Crystal engineering, Pharmaceutical cocrystals, Lexapro®, Entresto®, Celecoxib, Tramadol, Ertugliflozin, 5-oxo-proline, Lamivudine, Zidovudine.

INTRODUCTION

Crystallography is not new but it is ages, around 200 years ago and was thought that crystallography was more a subject within itself and was not having any practical implications in life, rather, chemistry can be used in extensive ways to influence life [1]. It was only after the discovery by Max von Laue that crystals diffract X-rays, this despairing attitude towards crystallography changed. To image the structure of matter at an atomic and molecular level has been of general interest. In general, crystallography till 1990′s was used as a tool and of relevance in structure of a molecule in the crystal in context of its solution chemistry by organic chemists. It was only with the advent of organometallic chemistry, the outlook for crystallography was significantly changed, as complex internal structure of organo-metallics could not be determined in solution through NMR and crystal structure was the only one way.The relationship between chemistry and crystallography can be expressed as interplay of both. The chemistry has to be with the molecules: the bonding of atoms to form a molecule and crystallography has to be with the crystals: which is the ordered arrangement of molecules. This interplay between the

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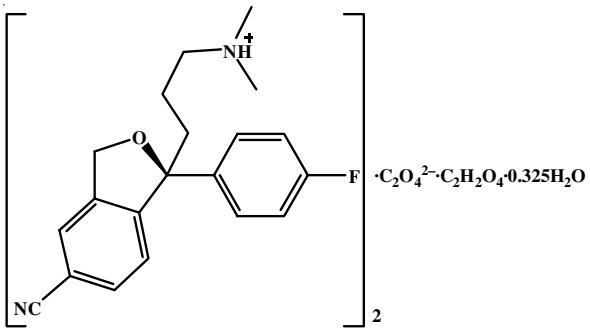
structure and the properties as a molecule and as a crystal came into existence as "Crystal Engineering".

The term crystal engineering was defined by Desiraju, crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in design of new solids with desired physical and chemical properties [2]. In the field of pharmaceuticals, crystal engineering laid a great impetus in development of new solid forms of Active Pharmaceutical Ingredients (APIs). By definition, pharmaceutical is a substance used in the diagnosis, treatment or prevention of disease and for restoring, correcting or modifying organic functions [3]. However, the marketed pharmaceutical consists of one or more APIs which are more often formulated into a suitable final form comprising inactive excipient. Most of the pharmaceuticals are administered orally in solid form which is most convenient and usually the safest dosage forms. The main problem with many of them is tackling of poor physico-chemical properties *viz*. solubility, stability, dissolution rate, hygroscopicity and permeability which remain of paramount importance [4]. The perspective behind the extensive search of new solid forms of APIs is to improve these physico-chemical properties [5]. Discovery of new chemical entity (NCE) is itself a difficult task and if fails in clinical development phase which are usually longer, results in significant losses to the company both in terms of time and cost [6,7]. There-fore, new methods are introduced for new solid form of APIs with significant chemical and legal advantages to extend the pharmaceutical space.

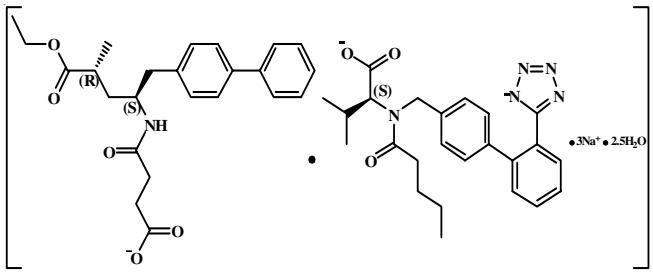
A consensus paper defines cocrystal as "solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts" [8]. If one of the components is an API, then it is recognized as a pharmaceutical cocrystal [9]. The literature is pouring out many pharmaceutical cocrystals over the last decade or so in search of some viable cocrystals which can be marketed as cocrystals [10-14]. Herein, some of the important examples of marketed and promising future pharmaceutical cocrystals are cited that are approved by United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMA).

Few examples of marketed pharmaceutical cocrystals

Escitalopram oxalate (marketed name: Lexapro®): Earlier considered to be a salt but later on it was established that it is a pharmaceutical cocrystal (escitalopram oxalate) and approved by the FDA in 2009, for the treatment of major depressive and anxiety disorders. Escitalopram belongs to the selective serotonin reuptake inhibitors [15].

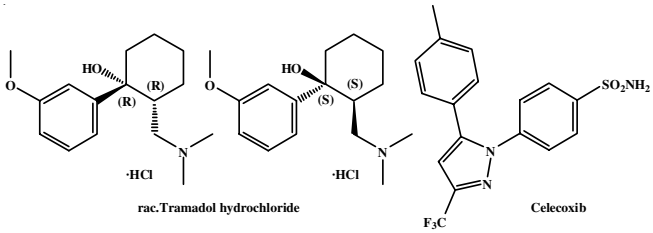


Sacubitril-valsartan (marketed name: Entresto®): A pharmaceutical cocrystal approved by the FDA in 2015 for the treatment of heart failure [16]. Entresto® is a fixed-dose combination product presented as film-coated tablets containing sacubitril and valsartan as active substances as a trisodium hemipentahydrate co-crystal by Novartis, Basel, Switzerland, the first drug in a class combining valsartan (angiotensin receptor) and sacubitril (inhibitor neprilysinis) to reduce cardiovascular mortality [16].

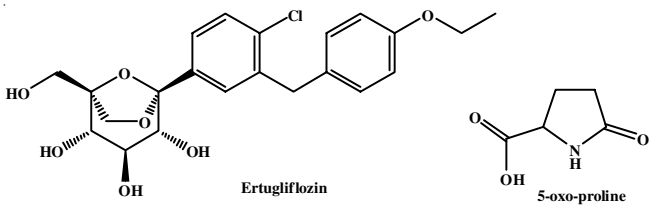


Few examples of promising future pharmaceutical cocrystals

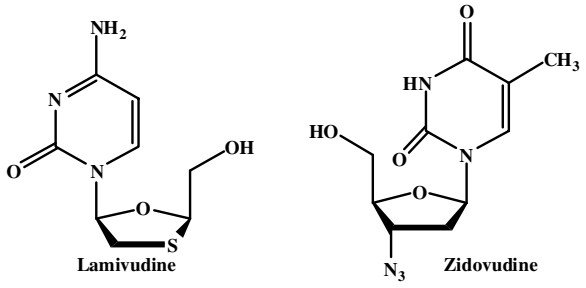
Celecoxib and tramadol: The successful phase II clinical trial of fixed dose combination of celecoxib and tramadol by Esteve and Mundipharma Laboratories GmbH show severe pain relief [17].



Ertugliflozin and 5-oxo-proline: A promising cocrystal of an anti-diabetic drug ertugliflozin with 5-oxo-proline is currently in the phase III clinical trials [18].



Lamivudine and zidovudine: Lamivudine (150 mg) and zidovudine (300 mg) given as a combination mixture by commercial name Combivir® registered toViiV Healthcare ULC. The lamivudine-zidovudine cocrystals for the treatment of HIV infection offer higher therapeutic efficacy [19].



Conclusion

The formation of cocrystals of existing Active Pharmaceutical Ingredients (APIs) with one another in order to enhance the solubility and bioavailability of the product and to be used as a combinational drug is a matter of higher importance. As it may lead to reduction in the amount of cost and effort put for New Chemical Entity (NCE) for pharmaceutical potential. Drugs with similarity in structures and 3D arrangements can be used for drug and drug synergy to obtain multi-drug cocrystal systems. Moreover, the development period for medications is reduced (including clinical tests), since cocrystals are not NCE and there is no structural modification of the APIs. Thus, they provide a unique opportunity to strengthen commercial formulations, but also to advance the development processes of substances that have not been developed due to low solubility or reduced stability.

REFERENCES

1. Maxims and Reflections of Goethe, Published Posthumously (1833).
2. G.R. Desiraju, Crystal Engineering: The Design of Organic Solids, Elsevier: Amsterdam (1989).
3. https://www.britannica.com/technology/pharmaceutical-industry.
4. J.D. Bernal and D. Crowfoot, The Structure of Some Hydrocarbons Related to the Sterols, *J. Chem. Soc.*, 93 (1935); https://doi.org/10.1039/jr9350000093.
5. (a) J.M. Robertson and J.G. White, The Crystal Structure of Coronene: A Quantitative X-Ray Investigation, *J. Chem. Soc.*, 607 (1945); https://doi.org/10.1039/jr9450000607.
   (b) J.M. Robertson and J.G. White, The Crystal Structure of Pyrene: A Quantitative X-Ray Investigation, *J. Chem. Soc.*, 358 (1947); https://doi.org/10.1039/jr9470000358.
   (c) J.M. Robertson, The Measurement of Bond Lengths in Conjugated Molecules of Carbon Centres, *Proc. R. Soc. Lond.*, **207**, 101 (1951); https://doi.org/10.1098/rspa.1951.0104.
6. FDA Challenges and Opportunity on the Critical Path to New Medical Products http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html#innovation.
7. J.A. DiMasi, R.W. Hansen and H.G. Grabowski, The Price Of Innovation: New Estimates of Drug Development Costs, *J. Health Econ.*, **22**, 151 (2003); https://doi.org/10.1016/S0167-6296(02)00126-1.
8. S. Aitipamula, R. Banerjee, A.K. Bansal, K. Biradha, M.L. Cheney, A.R. Choudhury, G.R. Desiraju, A.G. Dikundwar, R. Dubey, N. Duggirala, P.P. Ghogale, S. Ghosh, P.K. Goswami, N.R. Goud, R.R.K.R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A.S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C.M. Reddy, N. Rodriguez-Hornedo, R.D. Rogers, T.N.G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C.C. Sun, J.A. Swift, R. Thaimattam, T.S. Thakur, R. Kumar Thaper, S.P. Thomas, S. Tothadi, V.R. Vangala, N. Variankaval, P. Vishweshwar, D.R. Weyna and M.J. Zaworotko, Polymorphs, Salts and Cocrystals: What's in a Name? *Cryst. Growth Des.*, **12**, 2147 (2012); https://doi.org/10.1021/cg3002948.
9. Ö. Almarsson and M.J. Zaworotko, Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-Crystals Represent a New Path to Improved Medicines? *Chem. Commun.*, **17**, 1889 (2004); https://doi.org/10.1039/b402150a.
10. S.S.A. Abidi, Y. Azim, S.N. Khan and A.U. Khan, Sulfaguanidine Co-crystals: Synthesis, Structural Characterization and their Antibacterial and Hemolytic Analysis, *J. Pharm. Biomed. Anal.*, **149**, 351 (2018); https://doi.org/10.1016/j.jpba.2017.11.028.
11. S.S.A. Abidi, Y. Azim, A.K. Gupta and C.P. Pradeep, Cocrystals Of Indole-3-Acetic Acid and Indole-3-Butyric Acid: Synthesis, Structural Characterization and Hirshfeld Surface Analysis, *J. Mol. Struct.*, **1166**, 202 (2018); https://doi.org/10.1016/j.molstruc.2018.04.035.
12. S.S.A. Abidi, Y. Azim, A.K. Gupta and C.P. Pradeep, Mechanochemical Synthesis and Structural Characterization of Three Novel Cocrystals of Dimethylglyoxime with *N*-Heterocyclic Aromatic Compounds and Acetamide, *J. Mol. Struct.*, **1150**, 103 (2017); https://doi.org/10.1016/j.molstruc.2017.08.080.
13. R. Thakuria and B. Sarma, Drug-Drug and Drug Nutraceutical Co-crystal/Salt as Alternative Medicine for Combination Therapy: A Crystal Engineering Approach, *Crystals*, **8**, 101 (2018); https://doi.org/10.3390/cryst8020101.
14. A.A. Najar and Y. Azim, Pharmaceutical Co-crystals: A New Paradigm of Crystal Engineering, *J. Indian Inst. Sci.*, **94**, 45 (2014).
15. W.T.A. Harrison, H.S. Yathirajan, S. Bindya, H.G. Anilkumar and M. Devaraju, Escitalopram Oxalate: Co-Existence of Oxalate Dianions and Oxalic Acid Molecules in the Same Crystal, *Acta Crystallogr. C*, **63**, 129 (2007); https://doi.org/10.1107/S010827010605520X.
16. G. Bolla and A. Nangia, Pharmaceutical Cocrystals: Walking the Talk, *Chem. Commun.*, **52**, 8342 (2016); https://doi.org/10.1039/C6CC02943D.
17. C. Almansa, R. Mercè, N. Tesson, J. Farran, J. Tomàs and C.R. Plata-Salamán, Co-Crystal of Tramadol Hydrochloride-Celecoxib (ctc): A Novel API-API Co-crystal for the Treatment of Pain, *Cryst. Growth Des.*, **17**, 1884 (2017); https://doi.org/10.1021/acs.cgd.6b01848.
18. V. Mascitti, B.A. Thuma, A.C. Smith, R.P. Robinson, T. Brandt, A.S. Kalgutkar, T.S. Maurer, B. Samas and R. Sharma, On Importance of Synthetic Organic Chemistry in Drug Discovery: Reflections on the Discovery of Antidiabetic Agent Ertugliflozin, *MedChemComm*, **4**, 101 (2013); https://doi.org/10.1039/C2MD20163A.
19. P.M. Bhatt, Y. Azim, T.S. Thakur and G.R. Desiraju, Co-Crystals of the Anti-HIV Drugs Lamivudine and Zidovudine, *Cryst. Growth Des.*, **9**, 951 (2009); https://doi.org/10.1021/cg8007359.