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A brief review on pharmaceutical cocrystals

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Abstract

Poor aqueous solubility of an active pharmaceutical ingredient are the main constraints during the development of latest product. Various approaches are used for enhancement of solubility of poorly aqueous soluble drugs, but success of those approaches depends on physical and chemical nature of molecules being developed. Cocrystallization of drug substances modified the physicochemical properties such as melting tabletability, solubility, melting point, stability, bioavailability and permeability, while preserving the pharmacological properties of the active pharmaceutical ingredient. Cocrystals are multicomponent systems during which the main components are the active pharmaceutical ingredient and a coformer were present in stoichiometric ratio and bonded along side non-covalent interactions in the crystal lattice. This review presents a scientific overview of pharmaceutical cocrystals. The characterization of cocrystals have been summarized and different methods of cocrystal formation and evaluation have been explained.(1–3)

Keywords

Cocrystal, coformer, crystallization

Introduction

From recently discovered large numbers of drugs around 60-70% are related to the BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability) and cause difficulty related to dissolution, solubility, stability, therapeutic efficacy etc. To overcome this drawback various approaches are use they are as follow.

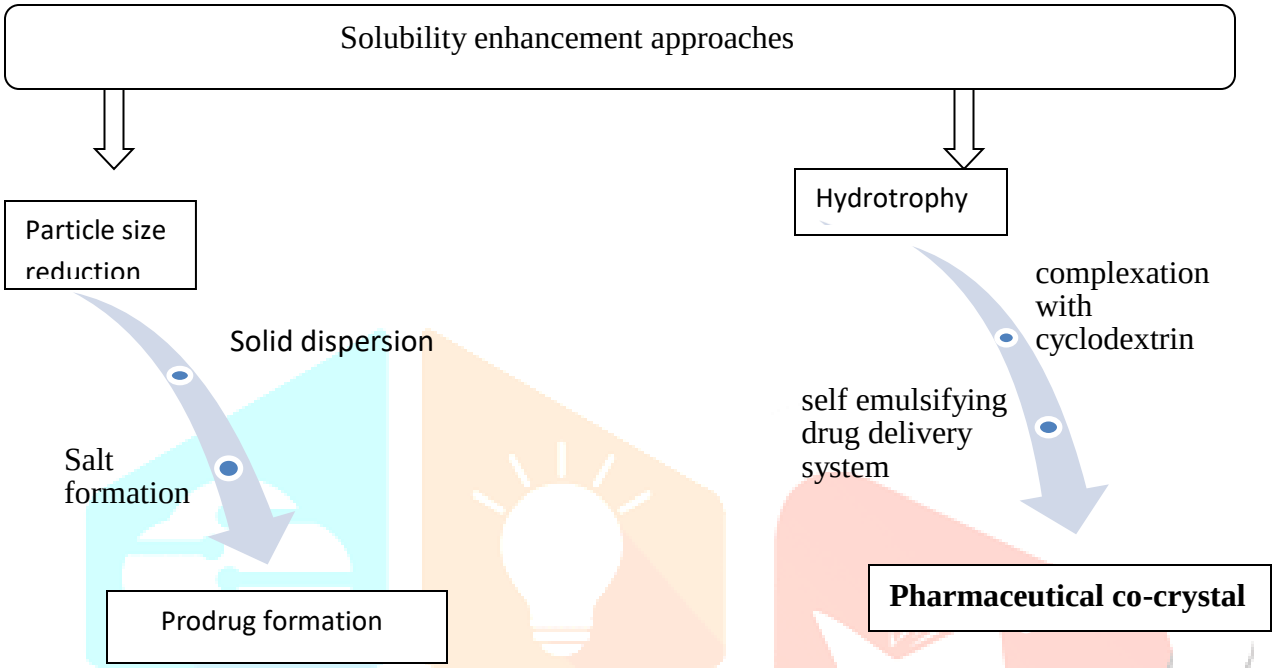

Fig: Solubility enhancement approaches.

Pharmaceutical co-crystal:

Cocrystals are solids that are neutral 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.(4)

Crystalline solids are formed when a solution becomes supersaturated with crystallizing solute(s) the vast majority of substances, if not all of them, will crystallize to form one or more crystalline phases under the right conditions. The cocrystals are coming under the classification of crystalline compounds. Cocrystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either an atom, ion, or molecule. Which represent the basic principles of hostguest chemistry. (5)

Physical property improvement is of particular interest to pharmaceuticals as the vast majority of medicines are delivered as solid forms. The physical properties of the solids contained within a pharmaceutical drug product will have a direct impact on the processing, delivery and, ultimately, performance of the medicine. To provide a classic example, crystal structure directly affects the solubility of a given solid in solution. Drug products require a certain solubility to be bioavailable in the body. It is estimated that 40 % of existing drug products and up to 90 % of new chemical entities have limited aqueous solubility 13 and hence cannot be delivered to the body using conventional techniques. Cocrystal formation with a suitable coformer offers

the potential of improved solubility via modification of the underlying crystal structure, thus potentially rendering the compound bioavailable.(6,7)

Crystalline form is important parameter in performance of the dosage form. It is most important in the molecular entity or compound which shows obstacles in the path of drug delivery and it is difficult in delivering the actual concentration of drug, such as low aqueous solubility, slow dissolution in GI fluid and first pass metabolism. As per nature of compound according to BCS classification system of drugs which shows stronger effect on the bioavailability. BCS class II compounds are water insoluble or having lower aqueous solubility such as nebivolol hydrochloride that needs to give orally in high amount. Cocrystal approach changes the physicochemical properties of compound and it is helpful to remove the obstacle in the path of delivering the proper concentration by changing dissolution, aqueous solubility,and first pass metabolism etc.of the compound. Cocrystal route is also applied for improving mechanical properties such as compressibility and stability of the compound. (8,9)

Method of preparation of cocrystals

Grinding method

Grinding methods have been widely used for the for the cocrystal formation over the past few years and found to be superior than other methods (solution or melt). Grinding techniques are of two types: neat or dry grinding and wet grinding. In dry grinding, drug and coformer are mixed together in a stoichiometric ratio and ground them by using either mortar and pestle or ball mill. Wet Grinding was performed in a similar manner that of neat grinding by addition of some drops of solvent in the mixture.(9–11)

Ultrasound assisted solution cocrystallization

Sonochemical method has been developed for the preparation of cocrystals of very small size i.e. for preparation of nanocrystals. In this method, API and cocrystal former are dissolved together in a solvent and the solution is kept in a sonoreactor to form the solution turbid. Cold water is supplied during the sonication to maintain the constant temperature of sonicator and prevent fragmentation. The solution is kept overnight for drying. Pure cocrystals were obtained by this method and the purity of cocrystals can be assessed by using X-ray diffraction study.(12)

Supercritical fluid atomization technique

In supercritical atomization technique, the drug and coformers are mixed with each other by using high pressurized supercritical fluid i.e. CO2. Cocrystals are prepared by atomizing this solution with the help of atomizer. In supercritical antisolvent (SAS) method, the cocrystals are prepared from solution by the antisolvent effect of supercritical fluid.(13)

Spray drying technique

In spray drying process, cocrystals are prepared by spraying the solution or suspension of drug and coformer with hot air stream to evaporate the solvent. This is the most preferred technology because this is a fast, continuous, and one-step process. Thus, spray drying process will offer a unique environment for the preparation and scale-up of cocrystals. (14)

Hot melt extrusion technique

In hot melt extrusion technique, the cocrystals are prepared by heating the drug and coformers with intense mixing which improved the surface contacts without use of solvent. The limitations of this method include both coformer and API should be miscible in molten form and not used for thermolabile drugs.(15)

Characterization of cocrystals

Powder X-ray diffraction

Powder X-ray diffraction data recorded by using powder Xray diffractometer (Bruker AXS D8 Advance, Germany). Conditions used for measurement: Si(Li) PSD detector, Cu X-ray source (λ=1.5406Å),3°to135°angularrange.PowderX-raydiffractiondata obtained compared with bulk drug and co-formers.(15)

Differential scanning calorimetry (DSC)

DSC peaks recorded by using differential scanning calorimeter (DSC 822e, Mettler Toledo, Switzerland). Accurately weighed sample (10–15 mg) placed in aluminium pan under nitrogen gas flow 20 ml/ minandscanned from50°C to450 °C(scanningrate 25°C/min), empty pan used as a reference.(13,16)

Infrared spectroscopy

Infra-red spectra recoded using FT IR (FT/IR-4000, Jasco, Japan). The spectra recorded in the region of 4000 to 400 cm−1 (high intensity ceramic source light source), DLATGS detector with 2 cm−1 spectral resolution. Data were collected from software. (17,18)

Evaluation of cocrystals

Solubility analysis

Excess amount of cocrystals placed in 10 ml distilled water in glass tubes sealed with aluminium foil. Resultant suspension stirred for 72 h and filtered. Filtrate obtained was diluted with distilled water and analysed spectrophotometrically using UV-spectrophotometer (V-630, Jasco, Japan).(8,15)

Intrinsic dissolution rate measurement

Intrinsic dissolution study was performed using USP apparatus II dissolution vessel (TDL-08L, Electrolab, India) containing 500 ml distilled water at 37 °C and 100 rpm. Dissolution studies for cocrystals lasted up to 60 min. Sample withdrawn at 10 min time intervals and measured by using UV spectrophotometer (V-630, Jasco, Japan) at specific nm.(8,10,19)

Applications

Cocrystallization has an advantage to optimize the physicochemical properties of drugs without altering the molecular structure of drugs. The chew over whether cocrystals or salts will have the desired properties depends upon the API and specific project.

Sometimes salts have better physicochemical properties such as salts have higher intrinsic solubility in water than cocrystals. Cocrystals with negative Δp*K*a value will give non-ionized drug when dissolved whereas salt will give ionized API, which is more soluble in water. Whenever dissolution rate of drug should be important rather than equilibrium solubility, cocrystals can be better than salt form of drug. Cocrystallization is an alternative way to enhance the solubility and bioavailability of poorly water soluble drugs, especially for those compounds which are neutral or weakly ionized in nature. Further, cocrystallization also offers

possibility of altering improving the melting point, tabletability, solubility, stability, bioavailability and permeability. as discussed in previous sections.(12,20,21)

Reference

1. Chaudhari S, Nikam SA, Khatri N, Wakde S. CO-CRYSTALS: A REVIEW. J Drug Deliv Ther. 2018 Dec 15;8(6-s):350–8.

2. Bhalla Y, Chadha K, Chadha R, Karan M. Daidzein cocrystals: An opportunity to improve its biopharmaceutical parameters. Heliyon. 2019 Nov;5(11):e02669.

3. Issa N. Towards more efficient screening of pharmaceutical cocrystals. :232.

4. Thompson L. Synthesis and structure determination of molecular cocrystals. :392.

5. Athira AS, Anu S, Seeja SR, Thaifa MS. A Review on Pharmaceutical Cocrystals. Int J Pharm Res Sch. 2018;7(3):1–17.

6. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. Cryst Growth Des. 2018 Oct 3;18(10):6370–87.

7. Nugrahani I, Komara SW, Horikawa A, Uekusa H. Composing Novel Diclofenac Potassium and l-Proline Salt Cocrystal as a Strategy to Increase Solubility and Dissolution. J Pharm Sci. 2020 Nov;109(11):3423–38.

8. Nikam VJ, Patil SB. Pharmaceutical cocrystals of nebivolol hydrochloride with enhanced solubility. J Cryst Growth. 2020 Mar;534:125488.

9. Zhang Y, Liu Y, Liu L, Feng Y, Zhang D, Wu L, et al. Tetrahydroberberine pharmaceutical salts/cocrystals with dicarboxylic acids: Charge-assisted hydrogen bond recognitions and solubility regulation. J Mol Struct. 2019 Dec;1197:377–85.

10. Jung S, Choi I, Kim I. Liquid-Assisted Grinding to Prepare a Cocrystal of Adefovir Dipivoxil Thermodynamically Less Stable than Its Neat Phase. Crystals. 2015 Nov 19;5(4):583–91.

11. Yuliandra Y, Zaini E, Syofyan S, Pratiwi W, Putri L, Pratiwi Y, et al. Cocrystal of Ibuprofen–Nicotinamide: Solid-State Characterization and In Vivo Analgesic Activity Evaluation. Sci Pharm. 2018 Jun 4;86(2):23.

12. Kumar S, Nanda A. Approaches to Design of Pharmaceutical Cocrystals: A Review. Mol Cryst Liq Cryst. 2018 May 24;667(1):54–77.

13. Chadha R. Novel Cocrystals of Glipizide: Green Supramolecular Mechanosynthesis. Arch Pharm Pharmacol Res [Internet]. 2018 Oct 13 [cited 2021 May 20];1(2). Available from: https://irispublishers.com/appr/fulltext/novel-cocrystals-of-glipizide-green-supramolecular-mechanosynthesis.ID.000511.php

14. Gadade DD, Pekamwar SS. Pharmaceutical Cocrystals: Regulatory and Strategic Aspects, Design and Development. Adv Pharm Bull. 2016 Dec 22;6(4):479–94.

15. do Amaral LH, do Carmo FA, Amaro MI, de Sousa VP, da Silva LCRP, de Almeida GS, et al. Development and Characterization of Dapsone Cocrystal Prepared by Scalable Production Methods. AAPS PharmSciTech. 2018 Aug;19(6):2687–99.

16. Machado Cruz R, Boleslavská T, Beránek J, Tieger E, Twamley B, Santos-Martinez MJ, et al. Identification and Pharmaceutical Characterization of a New Itraconazole Terephthalic Acid Cocrystal. Pharmaceutics. 2020 Aug 6;12(8):741.

17. Rama V, Vidavulur S, Tadikonda PV, Rajana N, Mittapalli S. Novel cocrystals of brexpiprazole with improved solubility. J Cryst Growth. 2020 Dec;551:125910.

18. Khan FM, Ahmad M, Idrees HA. Simvastatin-Nicotinamide Co-Crystals: Formation, Pharmaceutical Characterization and in vivo Profile. Drug Des Devel Ther. 2020 Oct;Volume 14:4303–13.

19. Ban E, An SH, Park B, Park M, Yoon N-E, Jung BH, et al. Improved Solubility and Oral Absorption of Emodin-Nicotinamide Cocrystal Over Emodin with PVP as a Solubility Enhancer and Crystallization Inhibitor. J Pharm Sci. 2020 Dec;109(12):3660–7.

20. Mukherjee A, Rogers RD, Myerson AS. Cocrystal formation by ionic liquid-assisted grinding: case study with cocrystals of caffeine. CrystEngComm. 2018;20(27):3817–21.

21. Mukherjee S. Crystal Engineering of Pharmaceutical Cocrystals. :144.