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Review Article

REVIEW ON BRIEF INTRODUCTION OF PHARMACEUTICAL COCRYSTALS AND ITS EVALUATION PARAMETERS

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ABSTRACT

Pharmaceutical cocrystals are promising technology which can be used to improve solubility of poorly aqueous compounds. The role of crystal engineering principles in selection of suitable coformers and nature of supramolecular synthons present within the crystals are described. In this review the success of numerous pharmaceutical cocrystals for improvement of the solubility and dissolution rates of poorly soluble drugs indicated using various examples taken from the literature. Furthermore, cocrystals of direct pharmaceutical interest, along with their in vitro properties and evaluation techniques are discussed highlighting the potential of cocrystals as an attractive route for drug development.

KEY WORDS: Pharmaceutical cocrystals, cocrystallization, solubility, stability, supramolecular synthons, evaluation parameters.

INTRODUCTION

Pharmaceutical cocrystals are defined as a multicomponent system that active pharmaceutical ingredient (API) and cocrystal former (CCF) at a specific stoichiometric ratio that are linked via intermolecular interactions, such as hydrogen bond, π-π packing and van der Waals forces.

Types of cocrystals-

1)Homomeric
2)hydrate/solvate
3)cocrystals
4)hydratedcocrystals
5)salt
6)salt hydrate
7)saltcocrystal
8)salt hydrate cocrystal

Pharmaceutical cocrystals can improve some of the physicochemical properties of APIs, such as solubility, dissolution rate, bioavailability and stability, without altering their chemical structures pharmaceutical cocrystal solubility comprises a dissolution-dissociation process, and its evaluation is based on kinetic solubility, thermodynamic solubility, and the intrinsic dissolution rate. Cocrystal are

suitable alternatives to salts for nonionizable APIs. Cocrystals in multiple stoichiometric ratio, in higher coformer concentration, can be expected to have favourable effect on solid state properties of the APIs.

COCRYSTALS-

The term "cocrystal" and design rules of hydrogen bonding of an organic cocrystal were first reported by Etter. Desiraju was the first who gave the supramolecular synthon concept of hydrogenbond formation in the crystal structures. In 2004, pharmaceutical cocrystals were described as a distinctclass of novel, crystalline materials which could alter the physicochemical properties of APIs and this wasthe beginning of the new era in crystal engineering and cocrystal formation. Duggirala and coworkers classified the cocrystals into molecular and ionic depending on the type of conformers [30]. Researchers proposed a broad definition of cocrystal that was consistent with the scientific literature. 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 [31]. In 2013, USFDA proposed a brief definition of cocrystal in the draft guidance as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" [32].

Examples of pharmaceutical cocrystals reported in the literature.

Drug	Coformer	Reference
Carbamazepine	4-aminobenzoic, saccharin, saccharin, salicylic, succinic, benzoic, ketoglutaric, maleic, malonic, formic, acetic, L-malic, L-tartaric,(+)camphoric,butyric	1,2
Curcumin	Resorcinol, pyrogallol	3,4
Danazol	Vanillin, 4-hydroxybenzoic acid	5,6
Indomethacin	Saccharin, nicotinamide, D/L mandelic, lactamide, benzamide	7,8
Itraconazole	Succinic, fumaric, L-malic, L-tartaric	9
Lamotrigine	Acetamide, nicotinamide, methylparaben	10
Meloxicam	Aspirin, salicylic, 4-hydroxybenzoic, glutaric, maleic, benzoic, fumaric	11 12
Nevirapine	Maleic acid, saccharin, salicylic acid,tartaric acid, glutaric acid	13
Paracetamol	Oxalic, theophylline, phenazine, naphthalene	14
Piroxicam	Saccharin, citric, adipic, succinic, benzoic, oxalic, salicylic, pyroglutamic acid	15,16
Pterostilbene	Piperazine, glutaric acid, caffeine	17,18

DIFFERENCE BETWEEN COCRYSTALS, SALT, SOLVATES AND HYDRATE-

Polymorphs are defined as the compounds which are present in different crystalline forms such as solvates or hydrates and amorphous forms. Polymorphs have different lattice arrangement and also, they have different physicochemical properties due to their crystal lattice structures. Salts are the compounds which are formed by complete transfer of proton from one compound to another. Salts and cocrystals can be differentiated based by a proton transfer from an acid to base. A complete transfer of proton takes place between acid-base pairs, whereas, no proton transfer occurs during cocrystal formation. Two components are bound to each other by non-covalent interactions such as hydrogen bonding, π-π stacking, van der Waal forces. A prediction can be made by ΔpKa value whether cocrystals are formed or not. It is generally accepted that a salt will be formed if the ΔpKa value is greater than 3 and ΔpKa value less than 0 will lead to the formation of cocrystals. This parameter is not accurate to predict the formation of cocrystals in solids between the ΔpKa values 0

and 3 but the possibility of salt formation will increase when the ΔpKa increases. Cocrystals and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates whereas those compounds which are solid at room temperature are called as cocrystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates [28]. Solvates/hydrates are commonly formed during the cocrystallization via solution or liquid assisted grinding and they can alter physicochemical properties of API's. Solvates/hydrates are quite unstable, because they lose solvent/water at high temperature and low humidity during storage. Example-Polymorphic cocrystals and solvates of caffeine and anthranilic acid were prepared by using different solvents via liquid assisted grinding [29].

SELECTION OF COFORMERS AND SCREENING OF COCRYSTALS-

A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former. Co-crystal former may be an excipient or another drug [18]. The USFDA had maintained a list of substances which is numbering in thousands and can be used as potential coformer for pharmaceutical cocrystals [19].

COMMON METHODS USED FOR COCRYSTAL SCREENING AND SYNTHESIS.

Method	**Mechanism**	**characteristic**
Reaction crystallization (RCM)	Solution process based on generating supersaturation with respect to cocrystal by dissolving reactants and or changing pH	Useful for both screening and synthesis; amenable for large and small scales
Solvo-thermal	Solution process based on generating supersaturation with respect to cocrystal through temperature change	Requires screening for solvents with similar reactant solubilities to minimize their crystallization
Sonic slurry	Solution process based on generating supersaturation with respect to cocrystal by subjecting a slurry of reactants to ultrasound pulses	May reduce the supersaturation for nucleation and increase nucelation rate
Co-grinding	Mechanical stresses enhance molecular molibity and lead to transformation of reactants to cocrystal	Solvent free method useful for screening
Liquid assisted grinding	Cocrystal formation through solution and/or solid phase mediated process	Useful for screening but requires larger amounts of materials than RCM
Moisture/vapor sorption	Solution process involves generating supersaturation with respect to cocrystal by vapor sorption of solid reactants	Suitable for screening by vapor sorption of solid mixtures
Melt crystallization	Cocrystal formation occurs through a melted phase	Useful for screening with small quantities of reactants by DSC and microscopy

Tween screw extrusion (TSE) and Hot melt extrusion (HME)	High screw mixing can lead to cocrystal formation with (HME) or without (TSE) melting reactants	Continuous, single-step, solvent free, and readily scalable process

DIFFERNT METHODS OF COCRYSTALS FORMATION-

Different types of solution methods such as solvent evaporation [35], solution crystallization technique, antisolvent addition [33], slurry conversion method [34] and reaction crystallization method [36] are discussed with suitable examples. Grinding methods are of two types: neat grinding and solvent drop grinding. Some newly emerging methods used for the formation of cocrystals are ultrasound assisted solution method, supercritical fluid atomization technique, spray drying technique [40], hot melt extrusion technique.

Solution-based methods:

Solvent evaporation method- Both API and coformer are dissolved in a suitable solvent and the solution is allowed to evaporate the solvent slowly. During dissolution, the functional groups in the drug and coformer interact with each other and form hydrogen bonds. This is most commonly used method for the preparation of cocrystals by researchers [39].

Solution crystallization technique- Drug and coformers are dissolved in boiling solvent with stirring and the boiling of the solution would be continued until the volume of the solution become small Slurry Crystallization-It is the process in which slurry is prepared by addition of different solvents in the mixture of API and suitable coformers. The solvent is decanted and the solid material is dried and characterized by different methods for evaluation. This method is selected for the preparation of cocrystals when the drug and coformer should be stable in the solvent.

Antisolvent addition method- coformers are dissolved in different solvents such as organic solvents and API is dispersed in the coformer solution by using dispersion homogenizer. This solution is then added to distilled water or suitable solution to precipitate the coformer on the drug.

Reaction crystallization method –It is used for rapid preparation of cocrystals at microscopic and macroscopic scale at ambient temperature in which nucleation and cocrystallization is based upon the cocrystal components and their solubility. The saturated solution of the lesser soluble component (drug) is made in methanol and filtered, and then the more soluble component (coformer) is added in an amount just under its solubility limit. Solution concentrations are monitored by HPLC throughout the crystallization process to evaluate whether the solid observed appeared to be a complex of the reactants (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) [38]. Grinding techniques are of two types: 1) Neat or dry grinding 2) 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 [37].

Ultrasound assisted solution cocrystallization:

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.

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.

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.

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 thermolabiledrugs [41].

EVALUATION OF COCRYSTALS-

FTIR spectroscopy-To predict the intermolecular interactions and compatibility study between drug and coformers. This technique is widely used to predict the chemical conformation of compounds. Pure drug, coformer, physical mixture and cocrystals are analysed by FTIR in the range of 400-4000 cm-1[42].

DSC-It is used for screening of cocrystal formation. Screening of cocrystals formation can be determined by the presence of exothermic peak followed by endothermic peak in DSC spectra. The presence of these peaks in the physical mixture of components indicates the possibility of formation of cocrystals. Pure drug, coformer, physical mixture and cocrystals were weighed out (1.5-2.5 mg) in aluminium pans and analysed with heating rates of 5-30° using similar empty pan as a reference. The nitrogen gas with flow rate 50 ml/min maintained the inert atmosphere. Melting point, glass transition temperature, polymorphic nature, heat of fusion, endothermic or exothermic behaviour can be determined by using DSC.

Solid-state NMR (SSNMR)-It is used to characterize solid phases that cannot be studied by SXRD. SSNMR was used to investigate the nature of complex by determining degree of proton transfer. Thus, SSNMR is an important tool for the identification of cocrystal or salt. SSNMR can also be used to evaluate the cocrystal structure by estimating hydrogen bonding and local conformation changes by couplings.

PXRD-It is commonly used for screening and determination of cocrystal structure [43]. The PXRD patterns obtained from diffractometer were compared to each other for analysing the structure of cocrystals. The different PXRD pattern of cocrystals from their components is the indication of cocrystal formation. Crystal structure of solids at atomic level cocrystals is determined by using single crystal X-ray diffraction (SXRD).

Dissolution study–It is used to determine the amount of drug release with time in dissolution medium. The dissolution studies for the cocrystals can be done within the suitable dissolution medium described in drug protocol of referred pharmacopoeia. The drug samples can be collected in the suitable quantity at predetermined time interval and examined with the help of HPLC or UV.

Solubility study –It can be assessed by Higuchi and Connors method for solubility determination. The solubility of pure drug, physical mixture and cocrystals can be determined in water or suitable medium. Drug sample and medium should be added in a conical flask, and should be shaken for 24 h at room temperature on rotary flask shaker. The entire samples should be protected from light by

wrapping the flask by aluminium foil if the drug is sensitive to light. After 24 h samples are filtered through Whatman filter paper and aliquots are suitably diluted and assayed by HPLC or UV at suitable wavelength.

Stability study-Provides the information about shelf life of drug products under different storage conditions. Drugs products should be kept in glass vials under variable environmental factors (such as humidity, temperature, light) for different intervals of time. After that, the samples are analysed for thermal study, drug release study, XRD study and FTIR study and compared with the results obtained before stability study [44].

APPLICATIONS

1) To optimize the physicochemical properties of drugs without altering the molecular structure of drugs. 2)Cocrystals with negative ΔpKa value will give non-ionized drug when dissolved whereas salt will give ionized API, which is more soluble in water.

3)To enhance the solubility and bioavailability of poorly water-soluble drugs, especially for those compounds which are neutral or weakly ionized in nature [24,25,26].

4) Cocrystallization also offers improving the melting point, tabletability, solubility, stability, bioavailability and permeability.

REFERENCES

1. S.G. Fleischman, S.S. Kuduva, J.A. McMahon, B. Moulton, R.D. Bailey Walsh, N. Rodríguez-Hornedo, M.J. Zaworotko, Crystal engineering of the composition of pharmaceutical phases: multiple-component crystalline solids involving carbamazepine, Cryst. Growth Des. 3 (2003) 909–919
2. S.L. Childs, N. Rodríguez-Hornedo, L.S. Reddy, A. Jayasankar, C. Maheshwari, L. McCausland, R. Shipplett, B.C. Stahly, Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine, CrystEngComm 10 (2008) 856–864.
3. P. Sanphui, N.R. Goud, U.B.R. Khandavilli, A. Nangia, Fast dissolving curcumincocrystals, Cryst. Growth Des. 11 (2011) 4135–4145. [23] R. Chadha, A. Saini, P. Arora, D.S. Jain, A. Dasgupta, T.N. Guru Row, Multicomponent solids of lamotrigine with some selected coformers and their characterization by thermoanalytical, spectroscopic and X-ray diffraction methods, CrystEngComm 13 (2011) 6271–6284.
4. S.L. Childs, P. Kandi, S.R. Lingireddy, Formulation of a danazolcocrystal with controlled supersaturation plays an essential role in improving bioavailability, Mol. Pharm. 10 (2013) 3112–3127.
5. M.P. Lipert, L. Roy, S.L. Childs, N. Rodríguez-Hornedo, Cocrystalsolubilization in biorelevant media and its prediction from drug solubilization, J. Pharm. Sci. (2015)
6. S. Basavoju, D. Boström, S. Velaga, Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization, Pharm. Res. 25 (2008) 530–541.
7. T. Kojima, S. Tsutsumi, K. Yamamoto, Y. Ikeda, T. Moriwaki, High-throughput cocrystal slurry screening by use of in situ Raman microscopy and multi-well plate, Int. J. Pharm. 399 (2010) 52–59.
8. J.F. Remenar, S.L. Morissette, M.L. Peterson, B. Moulton, J.M. MacPhee, H.R. Guzmán, Ö. Almarsson, Crystal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids, J. Am. Chem. Soc. 125 (2003) 8456–8457.
9. M.L. Cheney, N. Shan, E.R. Healey, M. Hanna, L. Wojtas, M.J. Zaworotko, V. Sava, S. Song, J.R. Sanchez-Ramos, Effects of crystal form on solubility and pharmacokinetics: a crystal engineering case study of lamotrigine, Cryst. Growth Des. 10 (2009) 394–405
10. M.L. Cheney, D.R. Weyna, N. Shan, M. Hanna, L. Wojtas, M.J. Zaworotko, Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics, J. Pharm. Sci. 100 (2011) 2172–2181.
11. M.L. Cheney, D.R. Weyna, N. Shan, M. Hanna, L. Wojtas, M.J. Zaworotko, Supramolecular architectures of meloxicam carboxylic acid cocrystals, a crystal engineering case study, Cryst. Growth Des. 10 (2010) 4401–4413

12. M.R. Caira, S.A. Bourne, H. Samsodien, E. Engel, W. Liebenberg, N. Stieger, M. Aucamp, Co-crystals of the antiretroviral nevirapine: crystal structures, thermal analysis and dissolution behaviour, CrystEngComm 14 (2012) 2541–2551.
13. S. Karki, T. Friščić, L. Fábián, P.R. Laity, G.M. Day, W. Jones, Improving mechanical properties of crystalline solids by cocrystal formation: new compressible forms of paracetamol, Adv. Mater. 21 (2009) 3905–3909.
14. S.L. Childs, K.I. Hardcastle, Cocrystals of piroxicam with carboxylic acids, Cryst. Growth Des. 7 (2007) 1291–1304.
15. P.M. Bhatt, N.V. Ravindra, R. Banerjee, G.R. Desiraju, Saccharin as a salt former. Enhanced solubilities of saccharinates of active pharmaceutical ingredients, Chem. Commun. (2005) 1073–1075.
16. S.J. Bethune, N. Schultheiss, J.O. Henck, Improving the poor aqueous solubility of nutraceutical compound pterostilbene through cocrystal formation, Cryst. Growth Des. 11 (2011) 2817–2823.
17. N. Schultheiss, S. Bethune, J.O. Henck, Nutraceuticalcocrystals: utilizing pterostilbene as a cocrystal former, CrystEngComm 12 (2010) 2436–2442.
18. Sekhon BS. Pharmaceutical cocrystal – A review. ARS Pharmaceutica 2009:50(3);99-117.
19. Najar AA, Azim Y. Pharmaceutical cocrystals – A new paradigm of crystal engineering. J Indian InstSci 2014:94(1);45-67.
20. D.P. McNamara, S.L. Childs, J. Giordano, A. Iarriccio, J. Cassidy, M.S. Shet, R. Mannion, E. O'Donnell, A. Park, Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API, Pharm. Res. 23 (2006) 1888–1897.
21. E. Lu, N. Rodríguez-Hornedo, R. Suryanarayanan, A rapid thermal method for cocrystal screening, CrystEngComm 10 (2008) 665–668.
22. D. Braga, S.L. Giaffreda, F. Grepioni, M.R. Chierotti, R. Gobetto, G. Palladino, M. Polito, Solvent effect in a “solvent free” reaction, CrystEngComm 9 (2007) 879–881
23. Martin FA, Pop MM, Borodi G, Filip X, Kacso I. Ketoconazole salts and cocrystals with enhanced aqueous solubility. Cryst Growth Des 2013:13;4295-304.
24. Qiao N, Li M, Schlindwein W, Malek N, Davies A, TrappittG. Pharmaceutical cocrystals: An overview. Int J Pharm 2011;419:1-11.
25. Lin HL, Hsu PC, Lin SY. Theophylline-citric acid co-crystals easily induced by DSC-FTIR microspectroscopy or different storage conditions. Asian J Pharm Sci 2013;8:19-27.
26. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceuticals cocrystals: a review of solvent free manufacturing technologies. Chem Commun2016;52:8772-86.
27. Childs SL, Stahly GP, Park A. The salt-cocrystalscontinuum:The influence of crystal structure on ionization state. MolPharm 2007:4;323-38.
28. Morissette SL, Almarsson O, Peterson ML, RemenarJF,Read MJ, Lemmo AV, et al. High-throughput crystallization:polymorphs, salts, cocrystals and solvates of pharmaceutical solids. Adv Drug Deliv Rev 2004:56;275-300.
29. Madusanka N, Eddleston M, Arhangelskis M, Jones W.Polymorphs, hydrates and solvates of a co-crystal of caffeine with anthranilic acid. Acta Crystallogr B StructSci CrystEngMater 2014:70;72-80.
30. Duggirala NK, Perry ML, Almarsson O, Zaworotko MJ.Pharmaceutical cocrystals: along the path to improvedmedicines. Chem Commun 2016;52:640-55.
31. Aitipamula S, Banerjee R, Bansal AK, Biradha K, CheneyML, Choudhury AR, *et al*. Polymorphs, salts and cocrystals:What’s in a name? Cryst Growth Des 2012:12:2147-52.
32. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm281764.pdf.
33. Chun NH, Lee MJ, Song GH, Chang KY, Kim CS, Choi GJ.Combined anti-solvent and cooling method of manufacturing indomethacin-saccharin (IMC-SAC) co-crystal powders. JCryst Growth 2014;408:112-8.
34. Zhang S, Chen H, Rasmuson AC. Thermodynamics and crystallization of a theophylline–salicylic acid cocrystal.CrystEngComm 2015;17:4125.

35. Lin HL, Hsu PC, Lin SY. Theophylline-citric acid co-crystalseasily induced by DSC-FTIR microspectroscopy or different storage conditions. Asian J Pharm Sci 2013;8:19-27.
36. Alhalaweh A, George S, Basavoju S, Childs SL, Rizvi SAA,Velaga SP. Pharmaceutical cocrystals of nitrofurantoin:screening, characterization and crystal structure analysis.CrystEngComm 2012;14:5078-88
37. Mukaida M, Watanabe Y, Sugano K, Terada. Identificationand physicochemical characterization of caffeine-citric acid cocrystal polymorphs. Eur J Pharm Sci 2015;79:67
38. Kotak U, Prajapati V, Solanki H, Jani G, Jha P. Co-crystallization technique its rational and recent progress.World J Pharm Pharm Sci 2015;4(4);1484-508.
39. Manin AN, Voronin AP, Drozd KV, Manin NG, Bauer-BrandlA, Perlovich GL. Cocrystal screening of hydroxybenzamides with benzoic acid derivatives: a comparative study of thermal and solution based methods. Eur J Pharm Sci 2014;65:56-64
40. Grossjohann C, Serrano DR, Paluch KJ, O'connell P, VellazarbL, Manesiotis P,*etal*.Polymorphism in sulfadimidine/4aminosalicylicacidcocrystals: solid-statecharacterization and physicochemicalproperties. J Pharm Sci 2015;104:1385-98.
41. Boksa K, Otte A, Pinal R. Matrix-assisted cocrystallization(MAC) simultaneous production and formulation of pharmaceutical cocrystals by hot-melt extrusion. J Pharm Sci 2014;103:2904-10.
42. Wu TK, Lin SY, Lin HL, Huang YT. Simultaneous DSCFTIRmicrospectroscopy used to screen and detect the cocrystal formation in real time. Bioorg Med Chem Lett 2011;21:3148-51.
43. Yadav S, Gupta PC, Sharma N, Kumar J. Co-crystals: Analternative approach to modify physicochemical properties of drugs. Int J Pharm 2015;5(2):427-36
44. Vaghela P, Tank HM, Jalpa P. Cocrystals: A novel approach to improve the physicochemical and mechanical properties. Indo Am J Pharm Res 2014;4(10):5055-65.