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Pharmaceutical Co-Crystals: An Overview on Synthesis and Regulatory Aspects

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ABSTRACT

Co-Crystals are crystalline materials formed by bonding between a drug and co-former. This alternative approach help to overcome many issues arise during preformulation like solubility, dissolution characteristics, compressibility, and product stability. The co-crystal engineering is done by following hydrogen bonding rules and molecular structure by using Cambridge structural database. co-crystals can be synthesized by solution mediated and solvo thermal methods. The formation of the crystals was analyzed by some analytical techniques like FTIR, DSC etc. The regulation of pharmaceutical co-crystals and their formulations shows considerable effect on development and quality control strategies and also to the value of intellectual properties.

Keywords: co-crystals, crystallization, Heterosynthons, stoichiometry

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INTRODUCTION:

Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice [1] in a definite stoichiometric ratio where the arrangement in the crystal latticeand is not based on ion pairing[2].

Pharmaceutical activeingredients (APIs) exists as polymorphs, solvates, hydrates, salts, crystals and amorphous solids. Each form displays unique physicochemical properties that caninfluence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs[3][4] .

The most thermodynamically stable form is the crystalline form of the compound[3][4][5]. An alternative method for enhancement of several pharmaceutical issues raised during preformulation[2]and formulation development e.g. by solubility, dissolution, bioavailability, chemical stability, decreasing hygroscopicity modulation is possible by cocrystallisation[6][7],while keeping the pharmacological effect of drug unchanged[8][9].where the components are arranged in the crystal lattice mainly based on ion pairing, the components in cocrystalsare assembled via weaker interactions, such as e.g., hydrogen bonding, π-π-stacking or van der Waals interactions[2].

Solubility is one of the important physicochemical properties that needs to be evaluatedduring the drug discovery and development process, since it is a significant factor that affects thedissolution rate and consequently, the oral absorption of the drug[10].

The substantial use of co-crystallization process in pharmaceutical industry has been accelerated by several widely publicized cases in the past few decades. For example, thalidomide was marketed as a sedative anti-nausea agent. However, while (R)-(+)-thalidomide served as a sedative, its optical isomer (S)-(−)-thalidomide was tragically found to act as a teratogen, resulting in the malformation of limbs in newborn. An Another example from1998, observing oral bioavailability problems due to polymorph of ritanovir in .an another example in 2008 leading to recall of rotigotine(Neupro) in the United States and in Europe because of the unexpected appearance of a new polymorph during storage. So maintaining the quality by increasing the stability parameters has got significance in the pharmaceutical industry [11] .

USES OF CO-CRYSTALS:

Improved bioavailabilityof an API[12]

It is importantthat the bioavailabilityof a drug should satisfythe regulations. a verylow bioavailability causesa drug ineffective whereas a high dose could betoxic. The bioavailability of an API is mainly dependent on its solubility and dissolution rates[9], which in turn, are dependent on the formulation of the API. The solubility of polymorphs are nearly 10 times more than amorphous form, whereas crystal forms has hundreds of times greater than amorphous form[9][13].

Increased resistance to hydrate formation[12][14]

Due to the presence of moisture aconversion of an API intoa hydrate form could bring about undesired physiochemical properties such as low bioavailability and can also implicate the processing, formulation, packaging and storage of the API.

Even after an API has been formulated into a drug product, there are some chances for cause of hydration. For example, using of some pharmaceutical techniques which employs water like granulation, spraydrying, film coating if hydrated excipients are used. hydration could be caused if the formulation itself has hydrated excipients, hygroscopic excipients or stored in moist conditions[14].

Improved compactionproperties for tableting

It has been estimated that only less than 20% of the Active Pharmaceutical Ingredients (API) can be processed into tablets viadirect compression since most ofthe API'slack properties required for direct compression like the flow, cohesion, packability, compactibility, compressibility or lubricating [15].

Recently, attemptswere made to produce alternative solid forms ofAPI'sthat are pharmaceutically acceptable, thermodynamically stable and better compaction properties. This was achieved by co-crystallization.

Several API'scan't be done into salt forms due to lack of acidic and basic groups on the molecule like paracetamol. a biologically safe molecules were produced using co-crystallization , such as paracetamol- trimethylglycine cocrystal[16].

DRUG SELECTION: [17]

The APIshould have at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphinic acid, phosphonic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, imine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, S-heterocyclic ring, thiophene, N-heterocyclic ring, pyrrole, 0-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, pyridine [18]to form bonding with coformers.

Drugs without tabletting properties and drugs without dissolution properties has wide probability of doing co-crystallization. [19]

CO FORMER SELECTION.

Supramolecular synthon approach which utilizes Cambridge Structural Database (CSD) which help in selection of bestco-formers for crystal form screening, Hansen solubility parameter and knowledge of hydrogen bonding between co-former and API[20]are effective tools in co-crystallization.

co-crystal former must be accepted by regulatory authority andhas at least one functional group selected from amine, amide, pyridine, imidazole, indole, pyrrolidine, carbonyl, carboxyl, hydroxyl, phenol, sulfone, sulfonyl, mercapto and methyl thio, such that the API and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions[18].

Examples [19]:benzoic acid ,succinic acid ,fumaric acid , glutaric acid ,glycolic acid ,sorbic acid, oxalic acid ,adipic acid ,maleic acid ,salicylic acid ,saccharin ,L-tartaric acid ,nicotinamide ketoglutaric acid, Form A , ketoglutaric acid, Form B , malonic acid, Form A ,benzoquinone,2,4-dihydroxybenozoic acid Form I ,2,4-dihydroxybenozoic acid, Form II ,4-hydroxybenzoic acid Isonicotinamide,2,5-dihydroxybenzoic acid ,2-hydroxybenzoic acid ,trans-cinnamic acid ,trans-2-hexanoic acid ,L-(+)-lactic acid ,L-(+)-tartaric acid ,(+)-camphoric acid ,4-hydroxybenzoic acid, Form A ,4-hydroxybenzoic acid, Form C .

DESIGN OF CO-CRYSTALS[21][3]

Co-crystallization produces novel pharmaceutical forms where the experimental work follows Hydrogen bonding rules and knowledge from cambride structural database.

Co-crystals consist of multiple components in given stoichiometric ratio, where different molecular species interact by hydrogen bonding and by non-hydrogen bonding.

The use of hydrogen bonding rules and synthons may assist in the designing of cocrystal systems and hydrogen bond patterns in a number of organic crystals[18].

The co-former selection is facilitated by understanding of the supramolecular chemistry [22]of the functional groups present in a given molecule is essential for designing the co-crystals. Supramolecular synthons that can occur In common functional group in orderto design new co-crystals and certain functional groups such as carboxylic acids, amides and alcohols are compliant for formation of supramolecular heterosynthon[12]. The strong hydrogenbond includes (N-H---O), (O-H---O), (-N-H---N,) and (O-H---N). The weakhydrogen bonds involvesthe –C-H---O and C-H---O=C.

HYDROGEN BOND DONORS AND ACCEPTORS:

The number of hydrogen bond donors and acceptors in a co-former and drug molecules also

Determinestheextent of success in co-crystallization [23][25]. Moleculesthat can form multiple hydrogen bonds are likely to form co-crystals with the co-former molecules.

Etter and Donohue framed HydrogenBond Rules to predict the circumstances under which hydrogen bond interactions that result into co-crystals .

These rulesare as given below:[24]

a. Mostly all good proton donors (such as –COOH, –NH4+) and acceptors (such as –OH, –NH3)

are utilized in hydrogen bonding.

b. Six-membered ringintramolecular hydrogen bonds (such as C-H. . . O) are formed first in preference to intermolecular hydrogen bonds (such as N-H. . . O andO-H. . . O).

c. The best proton donors and acceptors available after intramolecular hydrogenbond formationthen participate in intermolecular hydrogen bonds.

d. All acidic hydrogen atoms are included in hydrogen bonding in the crystal structure.

CRYSTAL FORMATION AND INFLUENCE OF VARIOUS FACTORS ON CRYSTAL HABITAT:

Habit describes the external shape of a crystal, whereas polymorph state refers to the definite arrangement if molecules inside the crystal lattice[3].

Thermodynamic parameter like solubility, kinetic parameters like super saturation, nucleation rate, dissolution rate, antisolvent addition rate, and evaporation rate phenomenon governs the crystallization[5].

CO-CRYSTALS SYNTHESIS: [26][27][28]

Co-crystals are crystalline materials that contain two or moredifferent molecular components in the same crystal lattice with well-defined stoichiometric ratios and these components are usually APIs and co-formers that are both solids at room temperature. Co-crystals have been prepared by solution, solid-state, or melt processes largely based on trial and error.

Solution-Mediated Processes:

The most generally used solution-based method to synthesize co-crystals is slow evaporation from solutions with equimolaror stoichiometric concentrations of co-crystal components[29,30].

Solvo-thermal methods:[29,31] heat is used to dissolve stoichiometric amounts of both components, thesolution is cooled, andthe co-crystals are then allowed to nucleate and grow.

Gas Anti Solvent (GAS) method: [32][33]

This approachhave reduced inorganic solvent use during co-crystal production. Specifically, carbon dioxide gasaddition effectively induces formation and precipitation from aqueous solution.

Itraconazole–succinic acid co-crystal can be effectively synthesized by this method.[26]

Spray-Drying or Freeze-Drying:[34]

Co-crystals, can also be formed by spray-drying or freeze-drying API–conformer solutions. These processes feature faster solute solidification compared to crystallization in aqueous solutions, which may promoteco-crystal production by reducing the phase separation and precipitation of low-solubility components.

Spray-drying is expected to facilitate the large-scale production of pharmaceutical co-crystals by fast, cost – effective solvent evaporation.

Freeze-drying is suitablefor the aseptic production ofinjectable solid formulations.

Thedrawback of this technique is generating less stable amorphous solids or metastable crystals

Co-crystalformation in the presence of a third component by a one-step spray drying process has the potential to reduce the number of unit operations which are required to produce a final pharmaceutical product[34] (e.g. by eliminating blending with excipient). Sulfadimidine (SDM), a poorly water soluble active pharmaceutical ingredient (API), and 4-aminosalicylic acid (4ASA), a hydrophilic molecule, were used as model drug and co-former respectively to form co-crystals by spray drying in the presence of a third component (excipient).

Example: CBZ–nicotinamide, theophylline co-crystals[35].

Freeze-drying is suitable for the aseptic production of injectable solid formulations. The drawback of this technique is generating less stable amorphous solids or metastable crystals[36].

Solvent drop grinding and solvent evaporation:[37]

Solvent drop grinding includes grinding of two materials together like solid state grinding with incorporation of small quantity of solvent. The solventadded act as catalyst. It is anticipated that this approach will open new opportunities in both the synthesis and characterization of co-crystals, regardless of the inabilities to characterize materials synthesized using this method by single-crystal X-ray diffraction.

Slurry Crystallization:[37]

Slurry crystallization is simple process which includes the addition of crystallization solvent in the components i.e. API along with its acceptable former. The selection of this process is mainly depends upon the physical stability of the crystallization solution to co-crystals and its solid former.

Hot melt extrusion:[38]

Extrusion is useful method for synthesis of co-crystals, it involves highly efficient mixing and

Improved surfacecontacts, Co-crystals are prepared without use of solvent. The selection of this method is primarily depends on thermodynamic stability of compound. This method was studied with the use of four models for co-crystal formation.

Solvent drop extrusion technique:

This method is used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in carvedilol and nicotinamide cocrystal formation[39]and synthesis of carbamazepine:4-aminobenzoic acid co-crystal system [40].

Evaporative Co-crystallization:[41]

Evaporative co-crystallization is a common method of generating co-crystals, typically employed for generating single crystal co-crystals suitable for diffraction studies to elucidate co-crystal structure. The technique involves the nucleation and growth of a co-crystal from a solution of both co-formers in a solvent, with super saturation provided by removal of the solvent from the solution via evaporation. Individual co-crystals, or the bulk crystal sample, should be harvested before the solution evaporates to dryness to ensure recovery of a clean crystal.

PHYSICOCHEMICAL PROPERTIES

Particle sizedetermination by microscopic studies:[42]

The particle size of the carbamazepine pure drug is found around 500-800 micrometers and CBZ : oxalic acid co-crystals were found less when compared to pure drug . the length of the needle shaped crystals were around 300-500 micrometres and the width is very less and nearly around 120 micrometer.

The needle shaped co-crystals has less particle size hence solubility might be increased[43].

Solubility: the solubility of Carbamazepine pure drug in water is 20mg per lit [17.7mg according to drug bank][44].The CBZ: Oxalic acid solubility has observed an increasein its solubility with 40 mg per litre.

ANALYTICAL METHODS:

Fourier transitioninfrared spectrometry:[42]

IR spectroscopy was conducted using a FTIR Spectrophotometer (Bruker opus) and background spectrumof carbamazepine and benzoic acidco-crystals was collectedatthe wavelength region of 4000–400 cm^{-1}under identical conditions.

Melting point apparatus:

Melting point is the physical property of solids, which is used to determine the purity of the product with sharp melts and narrow ranges .High melting point indicates the thermodynamically stability of the API's i.e.the co-former with high melting point may increase the thermal stability of a drug[14].

Co-crystals with low melting points can also be beneficial when dealing with thermo-labile drugs. The most commonly used techniques for determination of melting point and thermal analysis are differential scanning calorimetry(DSC) and thermal gravimetric analysis (TGA).

Differential scanning calorimetry:[42]

Thermal analyses of all CBZ co-crystal screening product were tested by a Perkin Elmer. About 10 mg of tested samples were put in aluminum pans and covered with a pierced lid. Measurements were carried out at a heatingof 10 ◦ C/min in the temperature range of 20 to 300◦ Cwith nitrogen flow rate of 20 mL/min.

Powder X-ray diffraction:

Thediffraction patterns of pure carbamazepine and co-crystalare obtained by using Bruker D8 Advance Diffractometer. The instrument was equipped with a fine focus X-ray tube and each sample was placed on to a goniometer head in a silicon sample holder, and data was collected while sample was monitored by spinning.[45].

REGULATORY ASPECTS OF COCRYSTALS:

The regulationof pharmaceutical co-crystals and their formulations shows considerable affectondevelopment and quality control strategies and also to the value of intellectual properties[46].

The APIs exist in different forms such as solvates, hydrates, salts and co-crystals by forming weaker bonds in which they show same therapeutic effect and broken while dissolution in stomach[47].An abridged application makes reference to the safety and efficacy documentation of an approved reference product containing the same active substance.

Polymorphic forms of a single entity active substance, or of salts, co-crystals, hydrates or solvates, will also be considered eligible for generic applications according to Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC 13(2)(b) [48].

It is crucial concerning the practical application of a co-crystal of a commercial APIis whether the co-crystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the co-crystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require.

In2012, the FDA (U.S. Food and Drug Administration) has issued guidelines to regulate the use of pharmaceutical co-crystals, and determines that a co-crystal should be considered as a drug product intermediate and not as a new API[49] . This decision give opportunitiesforuse of co-crystals in the pharmaceutical industry and eliminates the need for the co-crystal to go through clinical trials necessary if it had been considered as a new API, use of co-crystals of APIs for new chemical entities and genericproducts.

Draft version released in August 2016[48], FDA says it has provided clear guidelines about the regulatory classification of co-crystals and their relationship to solvates and hydrates.

According to FDA:

1. "From a physical chemistry and regulatory perspective, co-crystals can be viewed as a special case of solvates and hydrates, wherein the secondcomponent, the co-former, is not a solvent (including water), and is typically nonvolatile,"
2. co-crystals meeting its requirements are classified similar to polymorphs and are not regarded as new APIs.
3. "From a regulatory perspective, drug products that aredesigned to contain a new co-crystal are considered analogous to a new polymorph of theAPI,"
4. ''co-crystals that contain two or more APIs are considered to be fixed-dose combination (FDC) products rather than new APIs''.
5. companies already marketing drugs containing a material the agency previously considered to be a co-crystal can continue to do so, though new applications for those products should include evidence of the agency's previous co-crystal designation.
6. For drugs containing or claiming to contain a co-crystal, FDA says sponsors should submit evidence demonstrating that "both the API and the co-formers are present in the unit cell."
7. Sponsors should show that the API and co-former co-exist in the co-crystal and interact nonionicallyif both components have ionizable functional groups.
8. Sponsors should demonstrate that the API will be substantially dissociated from its co-crystal form before the drug reaches the site of pharmacological activity.
9. "Given that the interaction of the API with its co-former is of similar magnitude to the interaction of the API with solvents in solvates, an in vitro evaluation based on dissolution and/or solubility is generally considered sufficient to demonstrate that the API dissociates fromits co-former before reaching the site of pharmacological activity,"
10. An applicant can have the opportunity to claim for consideration of co-crystals with same approval or market authorization as given to an API.
11. The applicability of good manufacturing practices (GMP) for active substances or finished pharmaceutical products where co-crystals are produced in situ during process shall be taken into consideration

It concluded that the regulations of co-crystals understanding and other solid forms of API which may be of great value to the point of view to get a generic drug status for such forms as co-crystals are formed by non-covalent bonding.

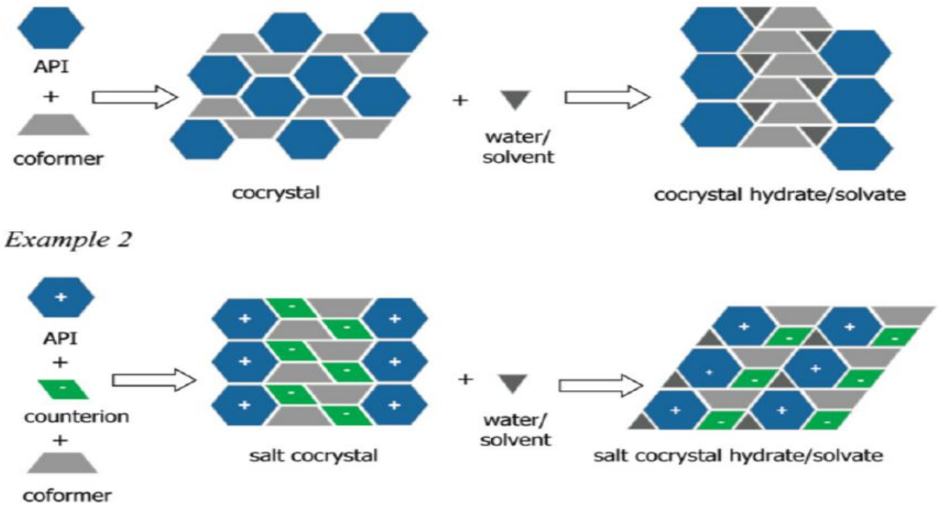

Figure 1: showing the formation of cocrystal hydrate/solvate. [50]

REFERENCES

1. Amidon et al: International Bioequivalence Standards: A new Era, TSRL Press, Ann Arbor, 2006
2. Reflection paper on the use of cocrystals and other solid state forms of active substances in medicinal products EMA/CHMP/CVMP/QWP/136250/2014
3. V. Yadav, A. S. Shete, A. P. Dabke, P. V. Kulkarni, and S. S. Sakhare
   Indian J Pharm Sci. 2009 Jul-Aug; 71(4): 359–370 ,Co-Crystals: A Novel Approach to Modify Physicochemical Properties ofActive Pharmaceutical Ingredients
4. Byrn SR, Pfeiffer RR, Stowell JG. Solid-state chemistry of drugs. West Lafayette: SSCI; 1999.
5. Brittain H, editor. Polymorphism in pharmaceutical solids. Vol. 95. New York: Marcel Dekker; 1999
6. J. V. D. Weerd, S.G. Kazarian, Release of Poorly Soluble Drugs from HPMC TabletsStudied by FTIR Imaging and Flow-Through Dissolution Tests, Journal of PharmaceuticalSciences, Vol. 94, No. 9, September 2005
7. C.A. Lipinski, Drug-like properties and the causes of poor solubility and poorpermeability, J. Pharmacol. Toxicol. Methods 44 (2000) 235-249.
8. Prabhakar Panzade, Giridhar Shendarkar, Sarfaraj Shaikh, Pavan Balmukund Rathi Pharmaceutical Cocrystal of Piroxicam: Design, Formulation and Evaluation2Adv Pharm Bull. 2017 Sep; 7(3): 399–408.
9. L.F. Huangand W.Q.Tong, Impact of solid state properties on develop ability assessment of drug candidates, Adv.DrugDeliver.Rev.,56(2004)321-334.
10. Williams, H. D.; Trevaskis, N. L.; Charman, S. A.; Shanker, R. M.; Charman, W. N.;Pouton, C. W.; Porter, C. J. H. Strategies to Address Low Drug Solubility in Discovery andDevelopment. Pharmacological Review 2013, 65, 315-499.
11. Recent Developments in the Crystallization Process: Toward the Pharmaceutical IndustryAuthor links open overlay panelZhenguoGaoabSohrabRohaniaJunboGongbJingkangWang bEngineering Volume 3, Issue 3, June 2017, Pages 343-353
12. ChaudhariShilpa *, NikamSarika, KhatriNeetu, WakdeShubham Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune- 411 044, Maharashtra, Co-Crystals: A Review, India, Journal of Drug Delivery & Therapeutics. 2018; 8(6-s):350-358
13. B.C.HancockandM.Parks,Whatisthe TrueSolubilityAdvantageforAmorphousPharmaceuticals?,Pharmaceut.Res.,17(2000)397-404.
14. R.K.KhankariandD.J.W.Grant,Pharmaceutical Hydrates,Thermochimica Acta,248(1995)61-79.
15. McCormick D. "Evolutions in direct compression". Pharm. Technol. 2005; 52: 52-62
16. Novel pharmaceutical cocrystal consisting of paracetamol and trimethylglycine, a new promising cocrystal former ,YusukeMaenoToshiroFukamiMasatoshiKawahataKentaroYamaguchiTatsuakiTagamiTetsuyaOzekiToyofumiSuzukiKazuoTomono
17. Pharmaceutical Cocrystals ,Elena I. Korotkovaa *, B. KratochvílbNational Research Tomsk Polytechnic University, Tomsk, 634050, Russia , Institute of Chemical Technology Prague, Technická 5, 166 28 Prague 6, Czech Republic.
18. Oern Almarsson, Magali Bourghol Hickey, Matthew Peterson, Brian Moulton, Nair Rodriguez-Hornedo Original Assignee: Transform Pharmaceuticals Inc, Univ South Florida, Univ Michigan, OernAlmarsson, MagaliBourghol Hickey, Matthew Peterson, Zaworotko Michael J, Brian Moulton, Nair Rodriguez-Hornedo
19. PoojaDhansukhlalVaghela et al. Cocrystals: A Novel Approach To Improve The Physicochemical And Mechanical Properties. Indo American Journal of Pharm Research.2014:4(10).
20. Sulbha R. Fukte, Milind P. Wagh, ShilpiRawat COFORMER SELECTION: AN IMPORTANT TOOL IN COCRYSTAL FORMATION ,International Journal of Pharmacy and Pharmaceutical Sciences ,Vol 6, Issue 7, 2014 Page: 9-14.
21. Nair RH, Sarah JN, Adivaraha J, Swarbreek, editors. Co-crystals: design, properties andformulation mechanism, in Encyclopedia of Pharmaceutical Technology. 3rd ed. Vol. 1. New York:Informa Healthcare; 2007. p. 615.
22. Aakeroy CB, Salmon DJ, Smith MM, Desper J. Cyanophenyloximes: reliable and versatile for hydrogen bond directed supramolecular synthesis of cocrystals. Cryst Growth Des 2006:6; 1033-42.
23. Analysis of Hydrogen Bonds in Crystals,Sławomir J. Grabowski
24. Crystal Engineering: From Molecules and Crystals to Materials [textbook] edited by Dario Braga, FabriziaGrepioni, A. Guy Orpen page number 92.
25. R Thakuria, Gauhati University, Guwahati, India B Sarma, Tezpur University, Tezpur, India, A Nangia University of Hyderabad, Hyderabad, India; and CSIR-National Chemical Laboratory, Pune, India Hydrogen Bonding in Molecular Crystals,
26. Encyclopedia of Pharmaceutical Technology, 3rd edition Edited by J. Swarbrick
27. S. Kumar and A. Nanda*Pharmaceutical Cocrystals: An Overview Department of Pharmaceutical Sciences, MaharshiDayanand University, Rohtak-124 001, India ,Indian J Pharm Sci 2017;79(6):858-871

28. Thakuria, R.Delori, A.; Jones, W.; Lipert, M. P.; Roy, L.; Rodriguez-Hornedo, N. Pharmaceutical Cocrystals and Poorly Soluble Drugs. International Journal of Pharmaceutics 2013, 453, (1), 101-125.
29. IndumathiSathisaran and Sameer VishvanathDalvi *Engineering Cocrystals of Poorly Water-Soluble Drugs to Enhance Dissolution in Aqueous MediumID
30. Childs, S.L.; Chyall, L.J.; Dunlap, J.T.; Smolenskaya, V.N.;Stahly, B.C.; Stahly, G.P. Crystal,engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. J. Am. Chem. Soc. 2004, 126, 13,335–13,342.
31. Bettinetti, G.; Caira, M.R.; Callegari, A.; Merli, M.; Sorrenti, M.; Tadini, C. Structure and solid-state chemistry of anhydrous and hydrated crystal forms of the trimethoprim-sulfamethoxypyridazine 1 : 1 molecular complex. J. Pharm. Sci. 2000, 89, 478–489.
32. Ober C. A., Gupta R. B.Formation of Itraconazole–Succinic Acid Cocrystals by Gas Antisolvent method , AAPS PharmSciTech., 13, 1396-1406 (2012).
33. Meena Kurup* and Arun Raj R "ANTISOLVENT CRYSTALLIZATION: A NOVEL APPROACH TO BIOAVAILABILITY ENHANCEMENT".Department of Pharmaceutical Science, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.jbps, 2016, Volume 3, Issue 3, 230-234.
34. International Journal of Pharmaceutics,Volume 536, Issue 1, 30 January 2018, Pages 467-477Production of cocrystals in an excipient matrix by spray drying Panel DavidWalshabDoloresR.SerranoabZelalemAyenewWorkuabBridA.NorrisabAnne MarieHealy
35. AmjadAlhalaweh, WaseemKaialy, Graham Buckton,HardyalGill,AliNokhodchi,andSitaram P. Velaga,TheophyllineCocrystals Prepared by Spray Drying: Physicochemical Properties and Aerosolization Performance
36. Mudit Dixit*, Parthasarthi K Kulkarni and PannerSelvam R Department of Pharmaceutics, J.S.S College of Pharmacy, J.S.S University, Mysore-570015, Karnataka, India. Review on: freeze drying as a crystallization technique Mudit Dixit et al./ Elixir Pharmacy 41 (2011) 5717-5730
37. COCRYSTALIZATION: AN ALTERNATIVE APPROACH FOR SOLID MODIFICATION MundheAkshayVitthalrao*, FuloriaNeeraj Kumar, BiyaniKailashRadheshyam,Department of Pharmaceutics, Anuradha College of Pharmacy, Chikhli, Dist.Buldana. Maharashtra, India-443201,Journal of Drug Delivery & Therapeutics; 2013, 3(4), 166-172
38. Dhumal RS, Kelly AL, York P, Coates PD, Para A. Cocrystalization and simultaneous agglomeration using hot melt extrusion. Pharm Res. 2010, 27(12), 2725–2733.
39. Fernandes, G.J., Rathnanand, M. &Kulkarni, V. J Pharm Innov (2018).mechanochemical synthesis of carvediol-Nicotinamidecocrystal by hot met extrusion method.
40. Palash Sanphuiand Geethabolla, Curcumin, a Biological Wonder Molecule: A Crystal Engineering Point of View ,Cryst. Growth Des. 2018, 18, 6370−6387
41. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and ApplicationsMaryamKarimi-Jafari, Luis Padrela , Gavin M. Walker, and Denise M. Croker* Synthesis & Solid State Pharmaceutical Centre (SSPC), Department of Chemical Sciences, Bernal Institute, University of Limerick, Limerick, Ireland ,Cryst. Growth Des., 2018, 18 (10), pp 6370−6387
42. Mounika P. et al / International Journal of Innovative Pharmaceutical Research. 2015,6(1),458-463. Preparation and Characterization of Novel Co-Crystal Forms ofFexofenadineP. Mounika1 *, S.Vijaya Raj1, G. Divya1, A. Gowramma2 and G.Vijayamma3
43. Text book of Biopharmaceutics and Pharmacokinetics By Bramankar Edited A.Treatise page no:19.
44. https://www.drugbank.ca/drugs/DB00564
45. PrabhakarPanzade,* GiridharShendarkar, SarfarajShaikh, and PavanBalmukundRathiPharmaceutical Co-crystal of Piroxicam: Design, Formulation and EvaluationAdv Pharm Bull. 2017 Sep; 7(3): 399–408.
46. Almarsson , Peterson ML, Zaworotko, Pat Anal. The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. 2012; 1(3):313-27. doi: 10.4155/ppa.12.29
47. Regulatory Classification of Pharmaceutical Co-Crystals, Guidance for Industry, U.S. Department of Health and Human Services,Food and Drug Administration,Center for Drug Evaluation and Research (CDER),August 2016,Pharmaceutical Quality/CMC,Revision 1.
48. http://circecrystal.com/fda-regulation-on-pharmaceutical-cocrystals
49. www.fda.gov/downloads/Drugs/Guidances/UCM281764.
50. Jampílek and Dohnal, licensee InTech.. Investigation of Carbohydrates and Their Derivatives as Crystallization Modifiers.