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CO-CRYSTAL TECHNIQUE OF SOLUBILITY ENHANCEMENT COMPREHENSIVE REVIEW

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ABSTRACT

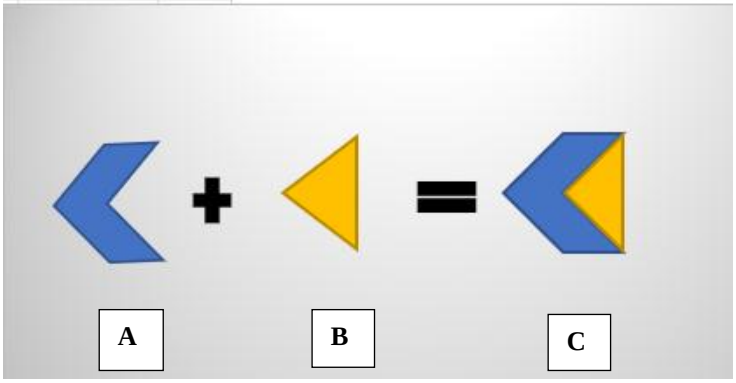
Co-crystal is a unique crystalline material containing two molecular components solid at room temperature having defined stoichiometric ratio. For administration of high doses of drugs such as HIV/AIDS, tuberculosis and other cocrystal are drug combination strategies used for the treatment and management of drug resistance and adverse reactions Improving the various parameters of a drug molecule such as solubility, melting point, pharmacokinetic, pharmacodynamic and bioavailability is possible through co-crystals. Various validation instruments such as x-ray diffraction and differential scanning calorimetry gives the overview of qualitative and quantitative aspects of co-crystals and evaluation of co-crystals. Attention of co-crystals in the discovery plays a role in drug design and development. A complete case study of theophylline and 5-nitrouracil regarding co-crystal. methodology and overview and methods of preparation of co-crystal.

KEYWORDS: Pharmaceutical Co-Crystal, Conformer, 5-Nitrouracil, Theophylline, Physicochemical properties.

INTRODUCTION

In 1894, Friedrich Wohler solved 1st cocrystal structure i.e., quinone and hydroquinone, but that is succeeded in the present century. In supramolecular chemistry co-crystal played a major role for the field of pharmaceutical, chemical and regulatory agencies.[2] As the efficacy of the active pharmaceutical compounds depends on the physicochemical properties/ pharmacokinetic and pharmacodynamic properties like solubility, Hygroscopic, dissolution, stability, bioavailability.[2,3] Cocrystal is a multiple component crystal of salts contributes key role in pharmaceuticals.[4] Accordingly to different literatures co-crystal develops a better drug product with a best and effective physicochemical product that does not change the pharmacological activity of the active pharmaceutical ingredient. Co crystallization possess the greater therapeutic activity. Two (or) more molecules together within a crystalline lattice that are non-turbulent are so called co-crystals. Solvates and hydrates are also included in co-crystals.[4,5]

Screening processes of crystallization process



A – Active pharmaceutical ingredients.
B – Conformers
C – Cocrystal

Solubility improvement enhances approaches upto the level as molecular level, colloidal level and particle level. After arrangement of co crystals melting point is the only property can be changed. Co crystal arrangement only depends on conformers.[2,3] The melting point of cocrystals changed with the change in the melting point of conformers and drug. The conformer must be generally regarded as safe and non-toxic compound.[34]

The conformers are selected based on the following theories:[6]

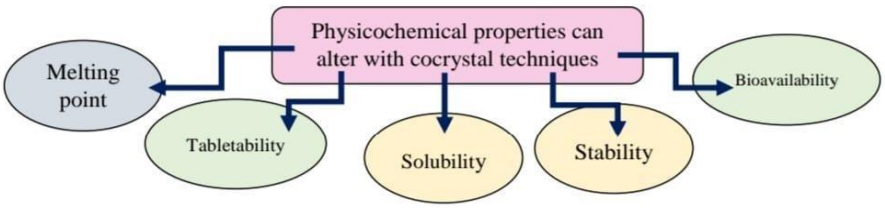
1 Pharmaceutical synthon approach
2 pka approach
3 Solubility approach
4. Pharmaceutical synthon approach: Deals with functional groups of conformer and API.
5. pka approach: Deals with the pka value of the conformer with API.
6. Supra molecular synthons: Deals with special arrangement of intramolecular.

Interactions in 2 different forms:[5,6,35,36]
Heterosynthon --- Increase the stronger bond interaction with Cocrystal form.[7]
Homosynthon --- Deals with the interaction between '2'similar (or) Identical functional group.

DEFINITION

Pharmaceutical co-crystal can be defined as crystalline material made up of API and one (or) more idiosyncratic co-crystal form, which are solid at room temperature.[1,2,3] APIs can exist in a variety of apparent solid forms along with polymorph, solvates, hydrates, salts, co-crystals and amorphous solids, Liquid solid compacts. Each form shows unique physicochemical properties which can be absolutely bioavailability, manufacturablility, purification, stability and other performance characteristics of the drug.[4,5,6]

PHYSICOCHEMICAL PROPERTIES AND APPLICATIONS OF COCRYSTAL METHODS



PHYSICAL STABILITY

A physical change is the modification about of state of material in absence of alteration within composition of as concern material.[4]

Physical characteristics include

1.	Hygroscopicity
2.	Solubility
3.	Hardness
4.	Plasticity
5.	Elasticity
6.	Melting point

MELTING POINT

Purity and thermodynamic stability API is determined by M.P. In designing cocrystals choosing appropriate co formers is essential.[4,37] Co crystal of Piroxicam is formed with Sodium acetate, Resorcinol, Nicotinamide amide, Saccharine sodium, Urea before it was low and later it escalated.[38]

SOLUBILITY

To date cocrystal is preferentially opted to ameliorate the solubility of pure API. Low aqueous solubility is hurdle to drug delivery and make the drug unsuitable for the usage.[4] Due to alteration in the fundamental structure of the starting substance. Solubility improved to some extent which further increases the bioavailability but intemperate increase production of a supersaturated, mixture /solution. 3 different cocrystals ezetimibe with methyl paraben used as conformer us 3 distinct techniques called solution crystallization, liquid co-crystallization, liquid assisted grinding, differential scanning calorimetry [DSC] and thermogravimetric analysis used for thermal and primary analytical tool respectively.[39] for conformatory analytical tool spectroscopic and crystallographic study is used equilibrium aqueous solubility of ezetimibe is amplified by 2fold in cocrystals produced by solution crystallization cocrystals produced was having same solubility that of ezetimibe which was synthesized reaction co crystallization technique. Co crystal showed enhanced dissolution profile which was produced by assisted grinding procedure.[40]

BIOAVAILABILITY

A new proposal called co crystallization in pharmaceutical industry that can enhance solubility and as a result bioavailability of API without adjusting the structural integrity. Marketed cocrystals formulation which include Entresto [Valsartan-sacubitri]ny Novartis and suglat [ipragliflozin-L-proline] by Astellas pharma and Kotobuki pharmaceutical.[4] Cocrystal that go through quick precipitation in course of dissolution of result in dehydrate of starting drug inside a aqueous of dihydromyricetin-caffeine as well as dihydro myricrtin

urea crystals. Precipitation dihydromyricetin is inhibited in the presence of polyvinyl pyrrolidone k30 which play role as crystallization inhibitor. Dihydromyricetin oral bioavailability is enhanced by 5 fold when two cocrystals are given at a dose of 2.0mg /ml of polyvinyl pyrrolidone k30 solution. Especially BCS class 2 and 4 drugs where strong focus is needed because they atre less soluble drugs. Clarithromycin drug with erythromycin, conformer form cocrystal by solvent evaporation technique which resulted in enhanced solubility of erythromycin resulted increased dissolution rate compared to pure drug.[40]

STABILITY

During formulation of new dosage stability is checked to obtain maximum pharmacological effect. Berberine chloride [BBC] has different pharmacological activities with fumaric acid cocrystals are discovered stoichiometric ratio of amount of FA and BBC is 1:2. The stability of cocrystal in high humidity or high temperature was enhanced as evidence. Improvement in stability of cocrystal in high temperature in high humidity was observed by stress test; thermal analysis and DVS test.[4]

MECHANICAL PROPERTIES ENHANCEMENT

Manufacturing dosage form mechanical properties are essential which include blending, coating, granulation, milling, tableting.[3] By altering the crystal packaging mechanical properties of the drugs are enhanced by co crystallization for tablet formulation deficient mechanical properties from barriers for numerous organic compounds. Mechanical strength in tablets is enhanced by putting in silicon dioxide and flowability is enhanced by addition of magnesium sterate by solvent evaporation procedure paracetamol with 5-nitroisophtalic acid form cocrystals which are excellent tabletability properties in contrast to either paracetamol or conformer.[5]

METHODS OF COCRYSTAL FORMATION[4]

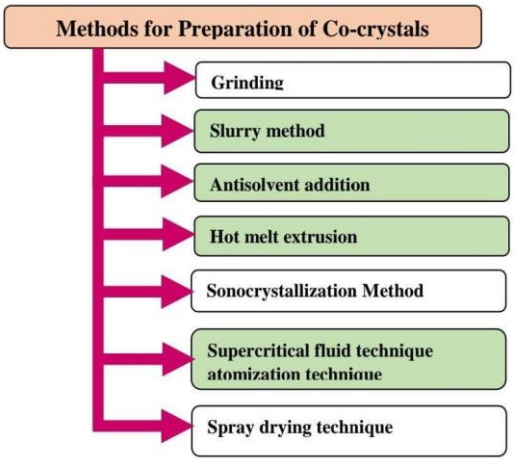


Figure 1: Methods of preparation of cocrystals

SOLID STATE METHODS

1 CONTACT FORMATION

In maintained atmospheric environment, API and conformer is mixed together /thorough. results in formation of cocrystals. in few instances, starting materials are grinded separately prior mixing. it has been demonstrated that the rate of crystallization in such situations is escalated rather than in situation where reactants are unmilled.[3] inflated co crystallization rates have been seen in conditions when higher temperature and higher relative humidity, nevertheless mechanical activation.[8]

2. SOLID STATE GRINDING[2,3,5]

It produces powders. two types are there.

[A] NEAT GRINDING

Co crystallization method in absence of a solvent.[2,3,5] stoichiometric ratios of solid materials are put together, pressed and crushed with help of motor and pestle, or vibrator mill or ball mill. grinding time span occurs between 30 to 60 mins. inappropriate settling generally leads to the non-successful cocrystal. increased surface area is observed by reducing the particle size this leads to interaction with materials for evolution of intermolecular bonding. it is easy, and it is faster preparation of desired cocrystal amorphous content formation leads to the crystalline defects, in similar way cocrystals are not completely formed due to incomplete conversion which further leads to combination of cocrystals and immoderate starting material to the final product which requires additional purification techniques to produce pure cocrystal.[7,9,10,11]

[B] LIQUID ASSISTED GRINDING

Neat grinding methods slight change leads to liquid – assisted grinding Mixing of very small fractions of solvent with two components while grinding leads to increase in kinetics of formation of cocrystals solvents play role of catalyst because it is present in minor amounts and is not observed in final product it also acts as media that ease molecular diffusion and in crystalline

system supramolecular selectivity is improved this method is used to prepare cocrystals in lesser time with high purity cocrystals of different polymorphic forms can be synthesized.[2,3,7] Constant of liquid-assisted grinding i.e it is scaled down technique, product purity is not up to the mark and energy utilization is high.[12,13,14]

[C] HOT MELT EXTRUSION TECHNIQUE

In this method, the drug and conformer is heated at a specific temperature so that there will enhanced surface contacts regardless / in the absence of solvent specific temperature is set so that matrix only is melted there is a requirement of catalysing agent to enhance the formation of cocrystals Heat screw extruder is used cocrystal of carbamazepine with cinnamic acid with help of single screw as well as twin screw have optimum dissolution rates compared with single screw cocrystals the merit this method has is no use of organic solvent, escalated conversion rapid operating time.[2,4] Ibuprofen with nicotinamide conformers resulted in cocrystals with this process varies process characteristics like temperature outline, screw speeder have been studied it was illustrated that co crystallization occurs only when eutectic point of physical mixture below barrel temperature.[7,15]

[D] SOLUTION BASED METHODS

For co crystallization from solution various kinds of techniques are present crucial driving force is supersaturation is co crystallization.[3,5] The concentration of target molecule and conformer should be considered It has been put forward to undertake polymorphic compounds [because they exist is different crystalline forms (more than one)] as co crystallizing components.[7]

3. SLURRY COCRYSTALLISATION

Methodology involves the formation of mixture of API and suitable conformers to these mixture different solvents are added which results in the formation of suspension A solid residue mixture is obtained by draining of solvent.[2,4,5,10,16]

4. EVAPORATIVE COCRYSTALLIZATION

This method involves the production cocrystals, especially single cocrystals which have suitable structures for diffraction analysis to illuminate of cocrystals. This method entail nucleation and growth of crystals Cocrystals of acyclovir are synthesized with succinic acid Physical features of drug has been enhanced Form 3 of which is an antileptic drug have different polymorphic forms.[3] Cocrystals are formed with the itaconic acid via solvent evaporation co crystallization with solvent acetone Acetone acts as solvent medium for the interaction between the conformer and drug the cocrystals produced showed in increased drug released when tested invitro when compared to the plain drug. In simple term this technique involves the dissolving the appropriate stoichiometric amount of conformer and drug in the solvent.[7]

5. COOLING CRYSTALLIZATION

It is rarely used technique production. Cocrystals of darunavir-succinic acid, in the cocrystals there is enhancement in micrometric characteristics, solubility, dissolution than its plain drug.[2] Cocrystals of carbamazepine, nicotinamide prepared from ethanol with enhanced properties.[3]

6. CRYSTALLISATION BY REACTION

Feed solutions of carbamazepine and saccharine are combined individually to produce cocrystals via reaction co crystallization. ternary phase diagram illustrates this method. It demonstrates a strong range of operation for the formation of cocrystals and anticipated association among induction time and supersaturation has to be indicated. At normal room conditions cocrystals of carbamazepine with nicotinamide conformers are generated via reactions co crystallization.[2]

7. ULTRA AIDED COCRYSTALLISATION

It is also known as sono crystallization which in used to generate nanocrystals. It involves the dissolving of drug along with conformer in the suitable solvent. The temperature of sonicator and forestall fragmentation should be maintained unchanged.[2,4] In course od irradiation energy is transmitted to sample that leads to quick incline in temperature within a short span of period due to this crystalline material will be melted. subsequently mixing of material occurs and results in rapid recrystallisation by cooling. For the nucleation procedure to occur in vapour phase the conformer selected should be in sublimable condition significantly in these technique pure crystals are produced.[17]

8. SPRAY FLASH EVAPORATION PROCESS

This technique is widely used in explosives to develop semi-crystalline nano composite which is dependent on superheated liquids flashing conduct. Which is liable to quick pressure decline. The technique indicates close interconnections among different drugs and conformer sets 9pairs0 eventually leads rapid rates of crystallization.[2,4] A low boiling point solvent (60degrees) with high pressure is selected into which the material is dissolved. Then in the chamber atomization occurs along heated hallow-cone nozzle. As a result of sudden quick fall in pressure the excessive heated solution becomes unstable thermodynamically, Latest energy is formed from excessive energy which results in generation of cocrystals.[17]

S.no	DRUG	CO FORMER	METHOD USED TO PREPARE	REFERENCE
1.	Piroxicam	Adipic acid, Benzoic acid, Citric acid, Hippuric acid, Malonic acid.	Dry grinding method	[4,20]
2.	Darunavir	Succinic acid	Cooling crystallization	[4,21]
3.	Aceclofenac	Sodium saccharin	Solvent-drop grinding method	[4,22]
4.	Clarithromycin	Urea	Solvent evaporation	[4,23]
5.	Danazol	Vanillin	Solution crystallization	[4,24]
6.	Felodipine	Xylitol	Wet co-grinding	[4,25]
7.	Fexofenadine	Tartaric acid	Solvent evaporation	[4,26]
8.	Simvastatin	Nicotinamide, Asparatame, Malic acid.	Solvent evaporation, Slurry, Liquid assisted grinding	[4,27,28,29]
9.	Prulifloxacin	Salicylic acid	Solution crystallization technique	[4,30]
10.	Carbamazepine	Succinic acid	Solvent-drop grinding method	[4,31]

CASE STUDY OF PHARMACEUTICAL CO-CRYSTALS

In 1950s by Higuchi and Roy conducted studies on pharmaceutical co-crystals on the context of APIs. A study 0n context of complex formation between pharmaceuticals and macromolecules are been conducted. A series of studies are reported by zerkowski et al which is the first application on pharmaceutical crystal engineering to the generation of pharmaceutical co-crystals.[5]

CO-CRYSTAL OF 5-NITROURACIL

Solvent molecules like dioxine, pyridine, formamide, DMSO and ethanol as well as piperazine, 3-Aminopyridine and diazabi-cyclooctane obtained by deliberate inclusion with cocrystals of 5-nitrouracil have been examined by x-ray crystallography.[5] The above solvents are used to retain the tape structure of the parent centric form of 5-nitrouracil by some modifications Guest molecules forming alternate tapes. molecules exhibit mixed compositions are observed in co-crystals involving formamide, ethanol, and 3-aminopyridine. The bonding patterns are observed in to be classified into 6 schemes. 3-Aminopyridine, or ethanol and water show quadruple type hydrogen bonding pattern. while, a network of acyclic tetrahedral pentamers of water is found in the cocrystal containing diazabicyclooctane and water. This case study deals with the hydrogen donor and acceptors are essential in the formation of cocrystals.[32]

CO-CRYSTAL OF THEOPHYLLINE

Theophylline is the used in the treatment of respiratory tract infections such as asthma. it is well known in the interconversion between crystalline anhydrate and monohydrate formation as a such of relative humidity (RH) The design of a consistent, reproducibility of an API in the drug development process is complicated due to the possibility of crystalline hydrate formation. There is a problem towards hydrate formation, in a range of common processing condition neither hydrate of anhydrates are highly stable. theophylline is the structural analogue of caffeine.[5] Theophylline co-crystal is prepared by using oxalic acid, malonic acid, maleic acid, glutaric acid, by solvent evaporation technique. At four different time points (1day, 3day, 1 and 7 weeks) the relative humidity stability comprised of the storage and subsequent PXRD analysis at four specific RH levels (0%, 43%, 75%, 98% RH) At 7 weeks of course study theophylline is converted to theophylline monohydrate at 75% RH and below. as well as zero or no formation of theophylline hydrate is formed or found at any case. The RH stability of theophylline is observed that co crystals demonstrates the improvement of physical stability, and also avoiding of hydrate formation. cocrystal form of theophylline is highly stable. This study demonstrates the use of cocrystals improves the physical improvement.[33]

ADVANTAGES OF CO-CRYSTALS

- Cocrystals are having an advantage like stable crystalline forms (comparative to amorphous solids), breaking and breaking of covalent bond is not necessary. All types of API (weakly ionizable / non-ionizable) have theoretical capability to form co-crystals.[3,8,19]
- In addition to enhance solubility, dissolution as well as bioavailability offered by normal co crystals MDCs (multi drug co-crystals) offer potential advantage of synergistic benefits.[3,8,19]
- MDCs improves or modifies the properties of the drug substances in the preparation of new strategies for the development of combination therapy.[3,18,19]
- Unstable compounds can be stabilized by multi drug co-crystals due to their intermolecular interaction.[3,18,19]
- For successful production of multi drug co-crystals use not only crystallography but also some other processes are also considered.[3,18,19]
- In pharmaceutical co-crystals production, the compatibility of two drugs, differentially solubility

and variations in dose must be considered.[3,18,19]

- Examples:
- 1. The 1:1 ratio of cocrystal acetaminophen and theophylline showed a better dissolution than that compared to physical mixture of these drugs.[3,18,19]
- 2. Due to its better potential therapeutic activity dapsone was co-crystallized by different Active Pharmaceutical Ingredient.[3,18,19]

CONCLUSION

In these review article we aim to outline the layout of co-crystal by working and spotlighting the most remarkable developments in comprehension on physicochemical properties of co-crystallization. In following this aim we were minded to set out and provide what we believed is the first physicochemical properties of co-crystal. It is understandable that the existing body of knowledge on physicochemical properties of co crystal formation is still adequate, particularly in contrast to the rapidly developing applications of co-crystal and fast evolution of modern methods of cocrystals. We expect that our try to give a co-crystal overview of physicochemical properties, pros and cons, applications and information given by us about co crystal will be of interest in developing audience of methods of co-crystallization and included case studies. An additional scientific investigation and communication gives rise to manage t and evolve an organized, ecological system of methods of co-crystallization and may be physiochemical properties, advantages and applications of co-crystallization.

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