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Review Article

An Updated Review on Pharmaceutical Co-Crystals: Characterization and Preparation

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ABSTRACT

Co crystals is an approach that can enhance the solubility of low water-soluble drugs (BCS Class-II) and It is the most prominent method that helps us achieve desired bioavailability of any drug because its multisection factor one of the section is API and the rest can be of different types of polymers according to its grade, class, applicability etc. this multi-component mechanism has a humongous outcome, likely by improving stability, permeability, therapeutic effect, and other pharmaceutical factors. Cocrystal is not the latest method, but its approach is advancing day by day, it was discovered many decades ago and it continuously improved from the day of finding this upgrade to get over the limitation of older methods of preparation of cocrystals. There are several methods to formulate older once are- solvent evaporation, slurry method, grinding technique and newer are-hot-melt extrusion method, spray drying method, and supercritical fluid technique. To determine its characteristics many techniques are available likewise DSC (differential scanning calorimetry), XRD (X-ray diffraction method), SEM (scanning electron microscopy method), infrared spectroscopy, etc. This review discusses types of cocrystals and their preparation methods, limitations, and applications in the Pharmaceutical field.

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Introduction

Years ago in the field of drug discovery, a huge number of research was carried out that resulted in finding newer molecules to treat diseases or disorders, it was a good sign for the development of human civilization, but several flaws limit the use of these new chemical entities practically, it has been reported that more than 50% of the drugs that are marketed about 90% of NCE(New Chemical Entities belongs to BCS Class-II or Class IV countered with solubility an low bioavailability problem despite having good therapeutic value [35]. Due to their problem, most pharmaceutical research industries hesitate to formulate these days. In the last two decades, several novel methods have been found that show better solubility as well as bioavailability of drugs[4], approach that has achieved great popularity for solubility enhancement over time are micronization, solid dispersion, cosolvency, complexation, salt formation, and self-emulsifying solid dispersion[1,2], although these approaches modify the physicochemical properties and improve solubility but have some limitations of their own out of these approaches cocrystal, is one method to improve solubility[3].

Cocrystals are exists in solid form with a monophasic crystalline material comprising more than two different chemical entities normally in a stochiometric ratio which are not in solvates nor simple salts [4]. It involves non-covalent interaction such as hydrogen bonds, Van der Wall's bonds, and ionic bonds in a crystal lattice, pharmaceutically cocrystals exist in a crystalline structure that is formed by an API and conformers that are generally solid at room temperature [5]. The available conformer greatly affects the physicochemical properties of API [6]. Hence selecting the appropriate conformer for understanding intermolecular interactions, the crystal engineering technique can be applied to constructing and modulating newer solid forms with fined tune properties [10]. Crystallization can be applied to API in the development of immediate-release or extended-release formulations [12]. The advantages lie with pharmaceutical cocrystals are that it improves the physical and chemical properties of API without affecting its pharmacological properties and improves melting point, stability, tabletability, bioavailability, permeability etc. [6,13].

Cocrystals

Cocrystals are the combination of two or more different molecules in a specific stoichiometric ratio in a crystalline lattice through non-covalent interactions like

hydrogen bonding, Van der Wall's interactions [30], etc. Mainly a cocrystal consists of an active pharmaceutical ingredient and a coformer that is pharmaceutically acceptable combined with the API through noncovalent interaction, at least one measure of physicochemical properties [32].

Physical Properties

Physical stability

A modification in the physical form of a substance without any alteration in the chemical structure is known as physical change, solid state materials have physical properties like hygroscopicity, melting point, hardness, solubility, plasticity, and elasticity. Among the approaches for enhancing physical stability cocrystallization technique is the promising one to improve the above physical characteristics of the drug and physical stability [1].

Melting point

Melting point is the key factor in the characterization of polymorphs of a compound [30], It is determined by the temperature at which the solid state is in equilibrium with the liquid state DSC and TGA (thermogravimetric analysis) are preferred techniques to obtain melting point data[32], high melting implies the thermal stability of the drug, cocrystallization has a big part in the improvement of low melting liquid drugs thermal stability by the inter portion of a suitable coformer in the crystal lattice, propofol is formulated as o/w emulsion because of its low melting point, which has its drawback that is stability[33], M.C Kellar et.al developed a stabilised solid form of propofol- Nicotinamide cocrystal which is stable at room temperature by adopting the cocrystallization technique[1].

Relative humidity

In presence of moisture can deteriorate the API, hence many of the studies have confirmed that cocrystals remain unaffected by the moisture, it has been observed that indomethacin-saccharin (1:1) cocrystals showed a very small quantity of water was absorbed when undergoing dynamic vapour sorption/desorption experiment [30].

Chemical Stability

A chemical stability study was conducted using accelerated stability conditions that are at 40 ^{o}C/ 75 % RH and 60 ^{o}C / 75 % RH [32], stability studies of co-crystal of monophosphate salt with phosphoric acid using 40 ^{o}C / 75 % RH and 60 ^{o}C / 75 % RH for 8 weeks reported to have no detectable degradation from these studies

it was noticed that cocrystal may have better chemical stability [30].

Solution Stability

It refers to the ability of the co-crystal to remain in the prepared form without returning to its crystal form, a solution stability test was conducted on 2:1 caffeine/oxalic acid co-crystals by preparing slurry with water at a suitable temperature for 48 hours and it was found that there was no alteration in the physical structure indicating the stability of co-crystals [30].

Solubility

Solubility is the thermodynamic equilibrium of solute between the liquid phase and solid phase, it has been reported that cocrystallization of a drug can improve the solubility [30], as per reports that solubility plays a major role in drug dissolution and bioavailability, there is a need for improving solubility hence poorly soluble drugs were formulated as co-crystals to improve their solubility when itraconazole co-crystal compared with crystalline itraconazole it has been observed that co-crystal itraconazole exhibit greater solubility in the crystalline form [32].

Tabletability

Co-crystallization significantly affects the crystal packing tabletability and compares the behaviour of drugs that are imported during the preformulation study, it was observed that the compaction behaviour of co-crystals of paracetamol with trimethyl glycine and oxalic acid was found to be better than pure crystalline drug [33].

Characterization

There are several methods of characterization of cocrystals, out of those methods few methods have been discussed here i.e., X-ray diffraction (XRD), differential scanning calorimetry (DSC), Raman spectroscopy and hot stage microscopy [5].

Hot stage microscopy

It is used to characterize cocrystals as a function of time and temperature. Hot-stage microscopy can visualise thermal changes such as melting point, melting range, crystal growth, and crystalline transformation [5]. Chemical analysis of thermally altered materials by suitable methods like HPLC, Raman and FT-IR helps in the detection of these changes. As certain cocrystals exhibit few physical stability issues, characterization of cocrystals must be done for further development of physical properties to stabilize the system [15].

X-Ray Diffraction

X-Ray crystallography can provide complete structural information on cocrystals. XRD can be performed by two different sampling techniques i.e., by taking powder or by taking a single crystal. Powder XRD is most used for the identification of cocrystals as different cocrystals are associated with different characteristic peaks. The limitation that is associated with single-crystal XRD is the procurement of a single crystal. For powder XRD, fine powder was collected by trituration, the single crystal XRD structural data provides structural proof as well as differentiates between cocrystals and salts [37]. It has been a very trusted method to determine three-dimensional structures [34].

Differential Scanning Calorimetry

DSC is used for the thermal analysis of the sample; the instrument was calibrated for enthalpy and temperature by using indium. Samples were placed in non-hermetic aluminium pans following an inert atmospheric condition and scanned from 30 ^{o}C to 350 ^{o}C at a temperature rate of 10 ^{o}C rises per minute. The data for each sample was collected in triplicate form [36,39,41].

FT-IR

Energy absorption and scattering by the chemical bonds of cocrystals are different from that of pure components helps in the identification of the structural behaviour of cocrystals. The IR spectrum of bands of cocrystal is different from that of API and coformer. The nature of interaction involved in the formation of supramolecular synthons can be studied through the evaluation of the effects exerted on patterns of molecular vibrations using IR and Raman spectroscopy.IR has been shown for a huge number of systems to differentiate between cocrystals and salts. Both the vibrational spectra help in identifying whether the formation is a cocrystal or salt. Apart from IR and Raman spectroscopy single-crystal XRD and solid-state nuclear magnetic resonance (ssNMR) emerged as the best technique for assessing the nature of the complex [37,38,40].

Solid-state NMR

The ssNMR has great potency to characterize cocrystal as this technique can particularly identify hydrogen bond which plays an important role in the creation of cocrystal. NMR shifts for hydrogen bonding protons are highly deshielded, covering nearly 10 ppm range in various organic and pharmaceutical cocrystals. When the molecule contains carboxylic acid groups, ^{13}C chemical shift analysis can determine the carboxylic acid and carboxylate group’s protonation and hydrogen bonding state. When nitrogen is

involved in a hydrogen bond, ^{15}N ssNMR analysis of chemical shift and editing of the ^{15}N spectrum are used to assess the protonation state [32,38-40].

Method of Preparation of Cocrystals

1. Solvent Method
2. Solvent Evaporation
3. Cooling Method
4. Anti-Solvent technique
5. Solid-state Technique
6. Solid-state grinding
7. Liquid-assisted Technique
8. Heat-induced Crystallization
9. Slurry technique
10. Twin screw Method
11. Freeze drying Method
12. Supercritical fluid
13. Laser irradiation
14. Crystallization by reaction
15. Ultrasound-aided crystallization
16. Spray Drying Process

Solvent method

In this method the driving force for the crystallization was supersaturation, this can be achieved by finding the suitable eutectic point for drug-conformer-solvents concentration, this method comprises three phases in a mixture solvent and the suitable condition is where the drug and coformer are under saturation or unsaturated mean while the cocrystals are at supersaturated. The drug and coformer are in the ratio of 1:1 and the eutectic represent the solution minima [1], where the solvent content at its lowest indicates solubility at its highest value, and the cocrystal can be stable if when the API or coformer will be less soluble, represents all the concentrations are laying in the eutectic points [13].

Solvent evaporation

It is the most widespread and trusted method for the preparation of the cocrystal in pharmaceutical research institutes [10]. In this technique the API and the coformer are solubilised in a common solvent the amount is considered according to the stoichiometric ratio and then the solvent was evaporated at a controlled temperature to prevent degradation this evaporation method results in the hydrogen bonding between the different functional groups and nucleation of coformer in the prepared cocrystals [5,15]. This method was commonly used in the analysis procedure of the X-Ray diffraction study [1].

Cooling method

It is less popular and used in the pharmaceutical preparation of minimal quantity cocrystals due to its time-consuming process, but it was most widely used in bulk preparation of purified crystals in this method the API got

crystalized by altering the solution temperature to below room temperature or less via supersaturation of solution [13,1,3]. An amount of the drug was dissolved in a particular solvent volume at 40.0 ± 0.5 ^{o}C. The solution was cooled in a water bath to 10.0 ± 0.5 ^{o}C with continuous stirring, at the cooling rate of about 0.25 ^{o}C/min. then the prepared crystals were recovered by vacuum filtration, then washed with distilled water several times, kept at 25-30 ^{o}C to remove the solvent present in them, and then kept in a desiccator [51].

Anti-solvent technique

This method, also called vapour diffusion, achieved a pure grade of cocrystals. In this technique, an anti-solvent was added to the solution in which the API was low soluble or insoluble resulting in the precipitation of the drug. A supersaturation was seen when the second solution was added to the first antisolvent [15]. In this method, an antisolvent was selected and in this, the API was solubilized in the ratio of 2:1(Antisolvent: API) and then another antisolvent or a solvent was selected to the coformer was dissolved after which at 40.0 ± 0.5 ^{o}C temperature both the solvent was mixed that resulting in the precipitation of the drug in form of cocrystals, then vacuum filter the crystals and wash them with distilled water three times then dried at room temperature [51].

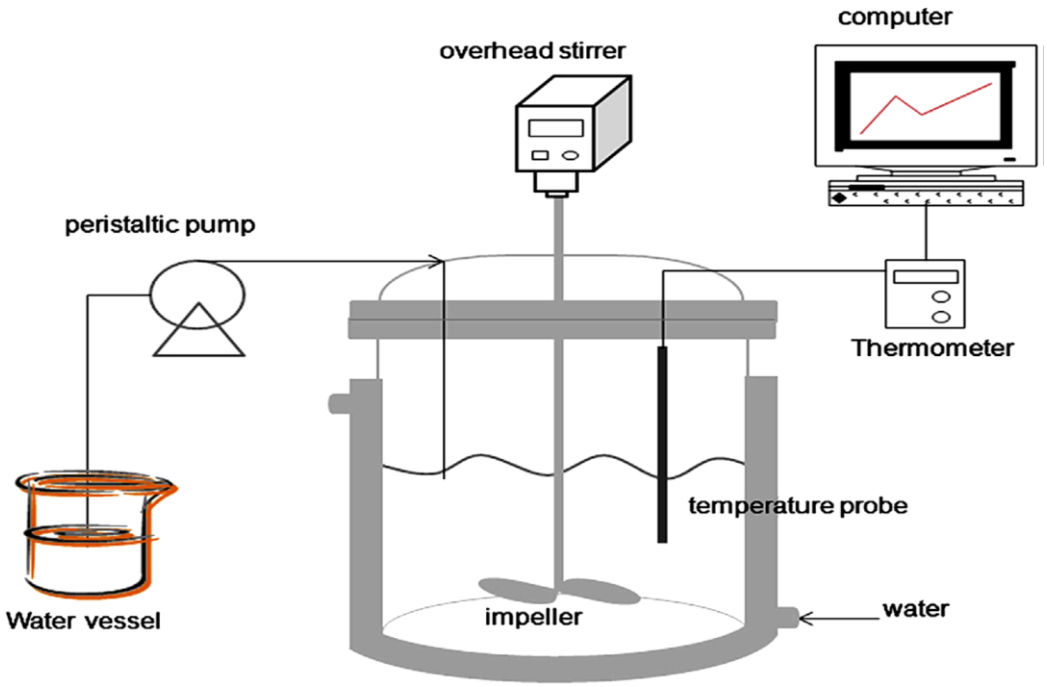

Figure 1: Instrumentation of anti-solvent method

Solid-state technique

In this method the drug and coformer are allowed to have physical contact with each other that resulted in the eutectic mixture or form of a liquisolid mass by evaporating the solvent the cocrystals are obtained, this method follows a mechanism like vapour diffusion of the two solids, moisture absorption, eutectic mixture formation, Amorphization etc. [1]. This technique was maintained under a fixed temperature and humidity to get high-quality cocrystals [4], there was no use of mixing or grinding method involved in making but in some cases it was seen to be used [26], it produced fewer organic cocrystals but in recent times it was seen that it has gained some popularity due to its fast and a minimum solvent used or no solvent use has attracted its useability [8,9], in this method it seemed that polymer alters the eutectic point of normal API and improve its physical stability [29].

Solid state grinding

In this method, a significant amount of drug and coformer was taken according to the stochiometric ratio and mixed with the help of a grinding instrument that helps in size reduction which helps in the covalent bonding of API and coformer this method has three phases of the process; rebuilding phase, transformation phase, and crystal disintegration phase although this technique has several limitations like polymeric transition during the process and incomplete crystal formation etc. [14,15,52].

Liquid-assisted technique

It is also known as kneading, solvent drop, and wet grinding [25]. This method was very useful to produce most pure cocrystals with a higher yield value, by the addition of solvent of less amount in the mixture of the API and coformer that Help to accelerate the cocrystal formation if the grinding speed and time were not taken care of then it results in faster crystallization of poor quality and quantity [1,3], and for grinding the instruments used like; mortar and pestle, using a ball mill, or using a vibratory mill. A small or stoichiometric amount of liquid (solvent) is added to the grinding mixture in liquid-assisted grinding or kneading [11]. For this method the API and the polymer should be compatible with each otherwise there will be no crystal formation [27].

Heat-induced crystallization

It was also known as the hot melt extrusion method or solvent drop method, in this method the drug and coformer were placed together and heat has applied that

resulting in the melting of the drug and coformer that help in crystal formation the temperature was maintained at 160-degree Celsius with continuous stirring till the mixing phase then cool it to get cocrystal this method helps in improving the surface contact and the selection of the drug a coformer should have thermostable in nature [2,23].

Slurry technique

This method involves the addition of the solvent into the cocrystal ingredients mixture that dissolves then mixing it with the help of a suitable mixer then evaporating the solvent at room temperature the amount of the drug and coformer ratio was selected from stoichiometric ratio. For this method, the material choice should be stable in the solvent and its limitation was it consumes more solvent and time [3,12,13,15].

Twin screw method

This method was first introduced by the author Medina et.al in 2009 [6]. In this method, the drug and polymer were selected by stoichiometric ratio and placed in an extruder with a heat applied and continuously stirring that help in crystal formation by eutectic mixture or by various means, as this method does not involve any kind of solvent, so it became environment friendly compared to other solvent methods [24].

Freeze drying method

In this method a drug and coformer solution was prepared with a common solvent used then it feezed rapidly times it goes below 0-degree centigrade Then to the solution apply a very high vacuum pressure that results in the sublimation of the frozen solution to gas, and the remaining solid powder has a low density and amorphous in the characteristics the process is also called as lyophilization this process is mainly for to safeguard the food items from its degradation [4,13,22].

Supercritical fluid method

This technique comprises the supercritical fluids that will dissolve the API and coformer in the high pressurized chamber and allow them for a while then release the pressure and it will result in the crystal formation the supercritical fluid used in this method was high-density liquid CO_2 this technique has gained popularity for preparation of nanocrystals from last several years, majorly CO_2 and H_2O are being used as supercritical fluids to prepare cocrystals, it follows the mechanism of atomization that help in the formation of the nuclei for the crystal growth [3.7,27].

Laser irradiation

In this method a High-frequency CO_2 laser was used to irradiate the powder mixture of the cocrystal ingredients and start their recrystallization to cocrystals, excitingly author has found that the polymer used has to go through a sublimation phase to initiate the crystallization that helps us to understand that the rearrangements between the molecule of API and Polymer and also the creation of the nuclei for the crystallization takes place in the vapour phase [53]. It follows the process as the high-frequency laser helps in rising the temperature that starts the melting of the polymer and rapid cooling helps in the formation of the crystals [15].

Crystallization by reaction

In this method, the author has reported the quick generation of crystals within minutes to an hour by following the method on microscopic and macroscopic scales under certain fixed conditions like temperature and pressure the nucleation and crystallization start with the effect of the cocrystal components on reducing the solubility of the molecular complex to be crystallized. This method is more important than others and is environment-friendly [20,28].

Ultrasound-aided crystallization

This method very used fully for the preparation of the nanocrystals the process follows the API and the polymer was mixed and dissolved in a solvent at a particular temperature then the solution was kept in a sonicator then the solution was treated with the ultrasound waves in a sonoreactor During this process the water temperature was maintained to prevent it from breaking then the solution was stored to evaporate the solvent resulting cocrystal formation [10,19,31].

Spray drying process

It is the most widely used method to get various products from food items to pharmaceutical drugs in this method a slurry mixture, emulsions, suspension, organic solvent mixtures, and aqueous mixtures are being used this process is not suitable for thermolabile drugs as it follows atomization and sprayed to the hot chamber with rapid drying with hot air or at a higher temperature [16-18].

Some preparation of cocrystals available in the market and their method are followed to obtain the crystals.

Table 1: Reported cocrystals of API with their conformer and method of preparation.

Sl. No.	Active compound	Coformer	Method	Reference
1	Ibuprofen	Nicotinamide	Solvent evaporation	[42]
2	Ibuprofen	Citric acid	Grinding	[43]
3	Simvastatin	Nicotinamide	Solvent evaporation	[44]
4	Ketoconazole	Ascorbic acid	Slurring method	[45]
5	Fluoxetine	Succinic acid	Solvent evaporation	[46]
6	Acyclovir	Nicotinamide	Solvent evaporation	[47]
7	Acyclovir	Theophylline	Solvent evaporation	[48]
8	Quercetin	Isonicotinamide	Solvent evaporation	[49]
9	Quercetin	Malonic acid	Grinding method	[50]

Conclusions

Poor aqueous solubility is the main disadvantage in successful drug delivery through the oral route. Several studies have been done to improve the oral bioavailability of drugs. In the last few years, pharmaceutical cocrystal becomes the centre of attraction for scientists and pharmaceutical industries to enhance the solubility of low water-soluble drugs by modifying their unwanted physicochemical properties. Pharmaceutical cocrystal is brought into consideration when a drug exhibits a complex and difficult-to-control polymorphism, when salts cannot be formed due to the neutrality of the compound or when the drug exhibit poor solubility, a literature survey shows that there is a limited example of pharmaceutical cocrystal available that reports on solubility and pharmacokinetic properties. As there is limited data available it cannot always say that cocrystal increase the solubility and bioavailability of drugs. It can be concluded that cocrystals can help in giving some extra chances to modify the physicochemical properties of API and denotes that their solubility and dissolution profiles are fully understood, and pharmacokinetic studies are performed to observe their in vivo exposure.

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