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A REVIEW ON COCRYSTALIZATION

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ABSTRACT

Solubility is almost doubled compared to pure drug co-crystals and they showed faster dissolution. Comparison with poorly soluble formulations Polymorphic and co-crystalline bioavailability was significantly improved by more than 10-fold. The second issue that needs to be addressed is Substance solubility may still be advantageous over drugs. A higher Ksp indicates a higher co-crystal solubility. It has two or more different molecules arranged in a single crystal lattice. permeability, solubility, Melting point, stability, tableting and bioavailability can be improved by pharmaceuticals Co-crystal. For co-crystals, the coformer can be considered an impurity, so the solubility of the starting material may change. The adoption of solvent droplet extrusion technology has increased versatility the best As a result, investigation of crystal synthesis using suspension crystallization started in 2018. Comparing the solubility of the co-crystal with that of the starting material. Pure solvents, which are often not taken into account in the stated solubility values. Additionally, several peaks are visible in the DSC (differential scanning calorimetry) scan. Differential scanning calorimetryA DSC thermogram is essential to show the melting endotherm maxima of a sample.

KEYWORDS: Pharmaceutical cocrystals, coformer, cocrystal characterization, crystal engineering.

INTRODUCTION

The therapeutic efficacy and production costs of solid dosage forms are greatly influenced by the physicochemical properties of active pharmaceutical ingredients (APIs), including stability, particle size, powder flowability, taste, hygroscopicity, solubility, and compatibility.

In oral medication administration systems, the solubility and rate of drug molecule dissolution are key factors in gastrointestinal absorption. However, at this time, 90% of novel chemical entities and 40% of medicines on the market fall under the Biopharmaceutical Classification System (BCS) II and IV classes, which are hampered by the problems of poor water solubility and low bioavailability.[1] Enhancing the fundamental qualities of an active pharmaceutical ingredient, such as bioavailability, solubility, flow properties, and thermal stability, is necessary for new technological developments in the pharmaceutical sector.[2] There have been many reports of solid-phase changes that improve the physicochemical properties of APIs. Along with the amorphous state, this category also includes several crystalline forms such polymorphs, salts, solvates, hydrates, and recently medicinal cocrystals. These can be used as a different approach to enhance certain physical properties of medicinal components.[3]

HISTORY

Etter was the first person to define the term "cocrystal" and to specify the techniques for how organic cocrystal-hydrogen bonds develop.[4,5] The notion of the supramolecular production of hydrogen bonds in crystal structures was first presented by Desiraju.[6] A new age of crystal technology and cocrystal generation began in 2004 when pharmaceutical cocrystals were identified as a distinct class of novel crystalline materials designed to change the physicochemical properties of APIs.[7]

PHARMACEUTICAL COCRYSTALS

Cocrystals are forms of crystalline matter that have two or more different molecules arranged in a single crystal lattice. Due to their ability to alter the physicochemical properties of drugs, cocrystals have grown to be of utmost significance in the pharmaceutical sector.[8] As of today, cocrystals are defined as "crystalline solids consisting of stoichiometric ratios of various constituents that form the crystal lattice via non-ionic interactions" and have been distinguished from salts and solvates since the 1990s.".[9]

PREPARATION OF CO CRYSTALS

Various methods employed in the preparation of co-crystals are shown in Recently Crystal pharmaceutical engineering has generated a lot of interest.[10]

1. SOLVENT EVAPORATION TECHNIQUE

Solvent evaporation is the most common and reliable method for producing co-crystals. In this operation, the drug and coformer are picked and dissolved in a common solvent in accordance with the correct ratios. The solvent is then evaporated at room temperature to form co-crystals. The solubility of the medications and coformer has a substantial impact on the choice of a common solvent. Functional groups in the drug and coformer molecules connect with one another through H-bonding and crystallise as a cocrystal. This method's primary drawback is that it uses more solvent.[1] The cocrystallization is influenced by the solvent choice, which may have an effect on the reactants' solubility. The cocrystal components need to be uniformly soluble in the solvent in question. When two incompatiblely soluble components cocrystallize, the less soluble one precipitates preferentially, resulting in a solid mixture of cocrystal and cocrystal components or the inability to form cocrystals.[2]

2. Hot melt extrusion

It has a very effective mixing and stronger surface contact, extruding is a technique that aids in the formation of a mutual crystal. The crystal is not created using a solvent. The major criterion for choosing this method is the compound's thermodynamic stability. The technique has been improved and its versatility has increased by using a solvent droplet extruding technology. This method has the benefit of allowing the procedure to be carried out at lower temperatures. Hot-melt extrusion was used to create carbamazepine and nicotinamide co-crystals utilising the polymer as the former. In a double extruder, the API and coformer are constantly crystallised together.[11]

3. Sonocrystallization Method

A sonochemical technique has been devised to produce organic cocrystals at the tiniest sizes. The main reason for developing this method was to make nanocrystals[12] The manufacture of caffeine-maleic acid crystals started with the use of ultrasonic technology.[13] Comparison of sonochemical methods with solvent pulverization for the production of caffeine, theophylline and L-tartaric acid as API has begun.[14]

4. Slurry Crystallization

Suspension crystallization is a simple method that involves mixing the API, the crystallization solvent and its formerly appropriate substances into the components. The physical stability of the crystallization solution to copper crystals and its former solid was a

key factor in the choice of this technique. With the best results, investigation of crystal synthesis using suspension crystallization has begun in the sixteen-crystal.[15] Slurry conversion tests involved the use of water and a number of organic solvents. After adding 100–200 ml of solvent, the resulting suspension was stirred at room temperature for a few days. Then the solvent was decanted, and the solid product was dried in the presence of a stream of nitrogen for a brief period of time. The remaining solids were subsequently described using PXRD analysis.[16]

5. SOLID STATE GRINDING

Alternative synthetic approach for solution-based cocrystallization process is solid state grinding. In a combination, particle size reduction is done, increasing the covalent reactivity. Compared to solution crystallisation approach, this process is more simple and gives more selectivity. Six crystals of sulfadimidine with anthranilic acid and salicylic acid were used to study the use of solid-state milling. Crystals of sulfadimidine-salicylic acid were ground with anthranillic acid. Salicylic acid is replaced by anthranilic acid because the hydrogen bonding structure of the two crystals is similar.[17] Cocrystals were produced by the solid grinding, which was not achievable by solution evaporation. This technique was employed to produce cocrystal phases with different coloristic features.[18]

6. Supercritical CO2-Based Methods

Using supercritical CO2 as a solvent or an anti-solvent in place of liquid solvents is a great way to produce crystals on a big scale.[19] Using supercritical CO2 as a solvent, the intriguing process known as Rapid Expansion of Supercritical Solutions (RESS) allows for the simultaneous micronization and cocrystallization of particles.[20] Other methods where supercritical CO2 has been used as an anti-solvent for the creation of cocrystals include Supercritical Fluid Enhanced Atomization (SEA), Atomization and Anti-solvent Crystallization (AAS), and Supercritical Anti-solvent Crystallization (SAS).[21,22,23]

Characterization of pharmaceutical cocrystal

It's crucial to ascertain whether and by how much a cocrystal is more soluble than the medication when one is discovered. It is not required to measure the entire phase, though. Cocrystal solubility graph to identify its zones of stability and solubility.[24] Techniques from crystallography are among the usual ways such as single-crystal X-ray diffraction and powder spectroscopic techniques (PXRD and SCXRD, respectively) FTIR (Fourier transform infrared), Raman spectroscopy and magnetic solid-state thermal techniques, resonance (solid-

state NMR), and such as optical hot-stage polarisation microscopy (HSM), analysis by thermogravimetry (TGA) and differential(**2**), x-ray photoelectron spectroscopy(XPS).

Raman spectroscopy

The constituent compositions of tablets incorporating cocrystals are revealed by Raman transmission investigations. This approach gives details regarding the Cocrystal lattice vibrations in solid states without significant excipient interference that frequently causes the analysis in terahertz, traditional Raman, and FT-IR spectroscopy. Some FT-IR, Raman, and terahertz mapping approaches Spectroscopies offer insightful data about the dispersion of ingredients in solid formulations. Tablet containing crystals Compositions of the ingredients are revealed via Raman transmission studies. Raman spectroscopy is growing in acceptance a technique for outlining crystal polymorphs found in medication compositions. This strategy provides information about the solid state cocrystal lattice vibrations without considerable interference from excipients.[9] The average Raman spectrum covers the low-frequency region below 400 cm1, which is unavailable to conventional IR spectrometers, and spans a range of a few tens of cm to around 4000 cm1.[16]

x-ray photoelectron spectroscopy(XPS)

This method can demonstrate the changes in a substance's chemical environment caused by the delivery of various energies (binding energies), which are needed to emit an electron from the nucleus at the atomic level. Fundamentally, The binding energy of photoelectrons released from a sample is recorded by XPS after having received an X-ray treatment. XPS is able to differentiate between the formation of a multicomponent salt or a cocrystal. robust, it is challenging to distinguish a salt-cocrystal continuum. The use of solid-state NMR (ssNMR) is a crucial method for obtaining more useful insights into the characterisation of crystals. The UK Model-KALPHA+ from Thermo Fisher Scientific was used for all investigations With regard to the load lock chamber (sample loading chamber) A 1.2 108 mbar vacuum and a 2 109 mbar vacuum were maintained for the chamber of the analyser a microfocus, monochromatic Al K-ray source with a spot size of 400 m, a power of 72 W, and 12 kV and 6 mA of current was applied to purchase. The samples' crystalline powders were pasted. placing the sample on a double-sided conductive carbon tapethat the XPS signal was totally covering the carbon tape, and not from the mounting tape, but just from the samples. The studied crystals were typically a few tens of micrometres in size(10−50 μm). High-resolution.[26,28]

Fourier transform infrared (FT-IR) spectroscopy

The chemical interactions between the drug and coformer can be evaluated using vibrational spectroscopic techniques, particularly those that involve hydrogen bonding.[32] On the other hand, Raman spectroscopy reveals rotational and vibrational modes. predominantly nonpolar functional groups that FT-IR cannot pick up at low frequencies. On the other hand, terahertz time-domain spectroscopy records frequencies in the range(0.3-333.6 cm-1 at 0.1-10 THz)bands represent the vibrations connected to accompanied by intermolecular interactions (hydrogen bonds, van der Waals, etc.).[27] The chemical conformation of substances as well as their compatibility and potential interactions with coformers can be predicted using FTIR spectroscopy. By analysing the creation of hydrogen bonds using FTIR spectroscopy, Aakeroy et al. were able to distinguish between salts and co-crystals because to the presence of the carboxylic functional group.[29]

Terahertz spectroscopy

Terahertz radiation, also known as THz waves, T-rays, T-lux, or THz light (1 THz equates to 1012 Hz, 33.3 cm-1, 4.14 meV, with a wavelength of 300 m), is a word used to describe electromagnetic radiation with a wavelength between 300 and 400 micrometres. The region was once known as the 0.1–10 THz range. recognised as the THz gap because of several challenges with sources and detectors. The THz frequency range's various molecular vibrations (such as molecular rotations, The significance of crossing (including torsional, crystalline phonon, intramolecular, and intermolecular) is highlighted this void.[30]

Single crystal x-rays diffraction (SCXRD)

This analytical technique is used to establish the phase of unit cells linked by co-crystals. The whole structural data of co-crystals may be accessible are derived from the words alone and powder. crystallisation using X-rays. While single crystal XRD is generally utilised to identify different co-crystals' structures by utilising distinct distinctive peaks, It uses a programme called "DIFFRAC.SUITE TOPAS." a problem in the main difficulty is locating a single crystal. The sample needs to follow Bragg's law (n=2d sin) since analysis.[10] In general, SCXRD was taken into consideration for analysis, particularly for smaller crystal samples. The typical anode has been replaced with a liquid metal jet that contains a LaB6 cathode, which eliminates the need to cool the anode before use.[31]

Powder X-ray Diffraction (PXRD)

Recent advancements in data processing provide reasonable structural information on cocrystals from powder XRD (PXRD) data.[9] Some of the cocrystals' phase change properties are observed using the PXRD technique.[34]

The PXRD provides data on the crystallinity of the solid phase. There are many examples in the literature where researchers have solved the crystal structure of cocrystals using information from powder x-ray diffraction.[8] As a result, distinct PXRD forms are correlated with different crystalline arrangements, which could be compared to the "fingerprints" of particular crystal segments. These chunks might stand in for various drugs or salts, solvates, polymorphs, and co-crystals of a particular medication. Therefore, PXRD could assess the varied phase transitions between the polymorphs of the same medication using a technique that can discriminate between salt and co-crystals, which are fundamentally distinct due to proton transfer in hydrogen bonding, at a range of temperatures.[31]

NMR spectroscopy

The stoichiometric ratios of the cocrystal phases can be determined via proton NMR spectroscopy, a type of nuclear magnetic resonance spectroscopy.[33]

Thermal Analysis

Differential scanning calorimetry (DSC) was performed using a Mettler-Toledo DSC 822e module (Mettler-Toledo, Columbus, OH). The samples were placed in vented, crimped aluminium containers. pans employed in DSC analysis. The typical sample size for DSC was 3-5 mg.

The temperature range of the heating curves was 30 to 300 °C, and the sample was heated at a rate of 10 °C/min. Samples were purged in a dry nitrogen is flowing at a rate of 80 mL/min.[28] The eutectic melting peak is the first peak on DSC thermograms that show two peaks, while the cocrystal melting peak is the second peak. Three peaks may occasionally be shown in DSC scans, the first of which is connected to eutectic melting once more, the second endotherm indicates that the excess of one of the components is melting. The third one concerns the crystallisation of cocrystals (cocrystal conformer). Additionally, the appearance Multiple peaks in DSC scans may signify a polymorphic change in cocrystals.[8]

Differential scanning calorimetry(DSC)

For depicting a sample's melting endotherm maximum, DSC thermograms are essential. By understanding melting endotherm maxima, provide you details on a novel, challenging phase.[35]

DSC also illustrates the peculiar behaviour of a crystalline mixture when heated and cooled. The heat of fusion and the heat of crystallisation can fluctuate with a change in concentration while utilising the DSC technique.[36]

Thermogravimetric analysis

Thermogravimetric analysis is one of the characterization techniques used in crystal engineering. This technique assists in figuring out working out techniques like sorption, absorption, and Other chemical reactions include chemisorption and heat desorption, breakdown, oxidation, and reduction. It mostly helps to find the thermal stability of the sample a vacuum, artificial atmosphere, or other setting where inert gas is expelled It is also possible to create without the control pressurethe incident.[2]

Differential thermal analysis

Differential thermal analysis is one of the thermoanalytical techniques that shares certain similarities with the DSC technique (DTA). DTA, on the other hand, allows us to measure the heat difference. between the interest sample and the reference sample using Variable temps DSC and TGA are reliable techniques for Nevertheless, cocrystal screening to determine thermal properties Crystalline, miscible, and solid-state transition properties A heated stage makes it easier to analyse morphology and nature, microscopy.[37]

Hot stage microscopy(HSM)

Hot stage microscopy (HSM), which enables the solid-state characterization of materials as a function of temperature and time, combines thermal analysis and imaging.[38] To study how the physical characteristics of solid materials vary with temperature and time, HSM combines microscopy with thermal analysis.

When heated, the drug crystals undergo changes that are both quick and obvious. viewed up close. Consequently, thermal changes such melting point, melting range, and Crystal growth, crystalline changes, etc. can be visualised. The HSM systems allow for controlled sample heating, which is placed on a glass slide, followed by a microscope examination. HSM

technology can be integrated with additional equipment, such as a digital spectrometer, a Fourier-transform infrared spectroscope (FTIR).[3]

ADVANTAGES OF CO CRYSTALS

A new crystal structure that is fully independent from any of the initial ingredients is produced through cocrystal formation. The physical qualities of any of the beginning materials have no bearing on or influence on the new set of physical attributes that are imparted by this new crystal structure.

1) Solubility

The improvement of the starting material's solubility has by far been the most common use of cocrystals to date, especially when the starting material includes an active medicinal ingredient. Due to the altered underlying crystal structure, a cocrystal will naturally have a different solubility than either of the original components. The change in solubility can go either way. Enhanced solubility is beneficial since it will increase the drug's bioavailability.[39] There are numerous other reports of increased solubility following cocrystal formation in the literature, but before we analyse the implications of cocrystal solubility, it is important to remember the real nature of solubility. In the case of cocrystals, the coformer can be viewed as an impurity and is thus likely to change the starting material's solubility. When cocrystal solubility is compared to the starting material's solubility in the pure solvent, this is frequently not taken into consideration in reported solubility values. to evaluate similarly.[40] In-depth research on cocrystal solubility has also been done by Rodriguez-Hornedo, who also put out the idea of a solubility product called K_{sp} that takes into consideration the relative concentrations of both cocrystal formers during cocrystal dissociation in a solvent.[41]

$K_{sp} = [A]^a[B]^b$

When activity coefficients are assumed to be one, superscripts refer to the cocrystal's stoichiometric number of a/b molecules. The strength of the drug and ligand interactions in cocrystal solid states relative to interactions with the solvent is reflected by the solubility product, which is closely associated to solubility. A higher K_{sp}indicates a stronger cocrystal solubility.[42]

2) Bioavailability

By altering medication solubility, pharmacokinetics, and bioavailability, crystals have the potential to improve drug delivery and clinical performance. When AMG 517, a strong and selective TRPV1 antagonist, is cocrystallized with carboxylic acid and amide coformers, its solubility and pharmacokinetics are improved, according to Stanton et al.[43] This strategy is especially crucial when the drug's cocrystal rapidly changes into a form with low solubility and is unable to maintain the required levels of solubility needed to ensure optimal absorption. Childs et al. used a suitable formulation that included a cocrystal, a solubilizer (1% vitamin E-TPGS (TPGS)), and a precipitation inhibitor (2% Klucel LF Pharm Hydroxypropylcellulose) to increase the solubility and bioavailability of a danazol:vanillin cocrystal.[44] Comparing this formulation to the poorly soluble danazol polymorph, the cocrystal's bioavailability was improved significantly by over 10 times.[45]

3) Controlled Release

Cocrystallization offers a flexible method for adjusting the physicochemical characteristics of pharmaceuticals, such as solubility and rate of dissolution. The rate at which the API dissolves in water or a buffer solution can change over time, especially depending on the coformer that cocrystallizes with it. In comparison to carbamazepine, cocrystals of carbamazepine and cinnamic acid produced by solvent evaporation displayed a greater rate of dissolution, solubility, and stability in water.[46] Additionally, cocrystals have the ability to slow the rate at which the original APIs dissolve. To maintain the water-soluble antiviral medication ribavirin's dissolving characteristic, Chen et al. adopted the cocrystallization method.[47]

4) Taste Masking

Oral disintegrating tablets must be prepared with fast-acting tablets that dissolve quickly. This method makes it possible to consume tablets without chewing them or drinking any water, allowing geriatric, paediatric, and patients on the go without access to water to use drugs. Using sugar-based coformers, cocrystallization may be a potential method for increasing the dissolution rate. The created cocrystal simultaneously benefited from enhanced dissolving rate and flavourmasking.[48]

Additionally, the trials on taste perception showed that the formulation was sweet since TMG was present in the structure.[49] Based on the automated sweetness tasting machine employed in this investigation, the produced cocrystal demonstrated increased solubility and sweetness

at the same time.[50] Propiverine was combined with organic acid solutions to form nine cocrystals. Propiverine salicylic acid cocrystals are less bitter than propiverine hydrochloride, according to the results of the usage of a taste sensor.[51]

5) Multidrug Cocrystals

In the medication formulation industry, combining numerous active pharmaceutical ingredients (APIs) into a single unit dose has grown in popularity. Multiple APIs can be combined in a single delivery system using salts, mesoporous complexes, coamorphous systems, and cocrystals.[52] MDC may have benefits over pure pharmacological components, including as improved solubility and dissolution of at least one component and improved bioavailability.[53]

6) Enabling in process separation and purification

To preferentially separate phenazine-vanillin cocrystals from their mother liquor, Lee et al. demonstrated a continuous cocrystallization technique at a scale of 90 mL/min.[54] In order to purify the API, Billot et al. reported on a slurry-based method for producing an API cocrystal at pilot plant size. They also demonstrated how to cleave the cocrystal afterward to liberate the API product.[55]

7) Mechanical properties enhancement

Tableting is the most prevalent pharmaceutical dose form due to its considerable technical and economic advantages. Some of these advantages are low manufacturing costs, fast production throughput, and simplicity of use, storage, and handling.[56] Cocrystallization has also been researched as a method to enhance the chemical and physical characteristics of powders, such as their mechanical strength and flow characteristics. For instance, cocrystallization with theophylline, oxalic acid, naphthalene, and phenazine increased the compression properties of paracetamol form I.[57]

CONCLUSION

The possibility of resolving the solubility issue in APIs is created by cocrystals. The controlled change of pharmaceutical properties as habit, bulk, density, solubility, compressibility, friability, melting point, hygroscopicity, and dissolving rate is made possible by the production of cocrystals. The development of cocrystals has enhanced preclinical performance, regulatory attention and intellectual property protection. There are numerous techniques in use now that improve the accessibility of API. Due to potential improvements

in their physical properties, cocrystals have a wide range of applications that are constantly expanding. There fore, cocrystallization may be able to address a number of both traditional and non-conventional issues facing pharmaceutical scientists today.

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