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Review Article

REVIEW ON COMPREHENSIVE DESCRIPTION OF DEVELOPMENT AND ASSESSMENT OF CO-CRYSTAL DRUG DELIVERY SYSTEM

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ABSTRACT

Over the past few decades, co-crystal Drug Delivery System (DDS) has attracted interest due to their potential to increase the solubility, stability, and bioavailability of medications that aren't sufficiently soluble. In this study, we factualized to develop a co-crystal chemical delivery system utilizing an experimental model. We utilized caffeine and succinic acid as model chemicals and prepared co-crystals utilizing different methods, including solvent evaporation, grinding, and spray drying. The co-crystals have been characterized utilizing X-ray powder diffraction, Fourier-transform infrared spectroscopy, and differential scanning calorimetry. The solubility and dissolution rate of the co-crystals has been evaluated in simulated digestive and intestinal juices. The outcomes showed that when compared to co-crystals made utilizing the solvent evaporation and spray drying procedures, those organized utilizing the grinding approach exhibited the maximum solubility and dissolution rate. This study underlines the potential of co-crystals as a workable method for enhancing the administration of pharmaceuticals that are not adequately soluble and provides a helpful experimental paradigm for the development of co-crystal chemical delivery systems.

Keywords: Slurry conversion, Cocrystal engineering, Antisolvent technique, Neat grinding, Solid dosage forms, Crystallization

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INTRODUCTION

The production costs of solid dosage forms and the therapeutic efficacy of Active Pharmaceutical Ingredients (APIs) are significantly impacted by the physical and chemical properties evaluation of APIs [1]. In oral medication delivery systems, solubility and rate of chemical dissolution have a substantial effect on gastrointestinal absorption. However, Biopharmaceutical Classification System (BCS) II and IV classes presently account for 40% of already available medications and 90% of newly created chemical entities, both of which have low aqueous solubility and limited bioavailability [2].

The atomic arrangement in the unit cell and crystal lattice has a direct impact on the properties of a particular crystalline substance. The crystal packing arrangements can be changed as a result; it is possible to change the physicochemical characteristics of solid chemical forms [3, 4]. Until now, a number of solid-state techniques have been used to adjust the characteristics of APIs, like salts, polymorphs, hydrates, solvates, and cocrystals [5-10].

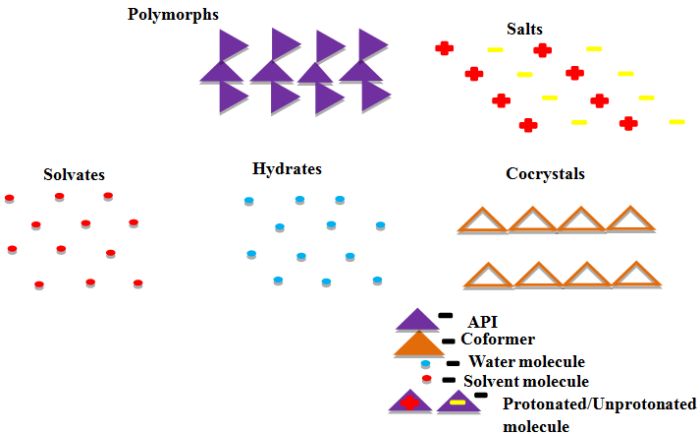

Fig. 1: Shows the difference between co-crystals and others [1]

For instance, only substances with the right ionizable groups may form salts, and hydrates and solvates often lose their stability over time because aqueous and solvent substances are prone to loss. In contrast, any API may create cocrystals when working with the right coformer. Pharmaceutical cocrystals have received focus from the pharmaceutical company and academia in the previous 20 y because they can change the crystal structure of APIs without changing their pharmacological characteristics, hence improving their physicochemical properties [11, 12]. Several pharmaceutical crystals, like Steglatro, have been authorized thanks to the advancement of the cocrystal sector, and others are now undergoing clinical trials [13-16].

Cocrystals, according to the FDA, are "Crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that is associated by nonionic and noncovalent bonds." The molecules could be readily soluble coformers, which are typically

organic compounds that have received the GRAS (Generally Recognized as Safe) designation [17]. Cocrystal engineering has been recognized as a promising method to enhance the physicochemical characteristics of medicines since the early 2000s, which was reflected in numerous exemplary pharmaceutical cocrystal papers [9, 18-20].

We searched the studies in three databases, including Google Scholar, PubMed, and Elsevier websites, for the last ten years to find all related articles on the development and assessment of the Cocrystal drug delivery system. Papers with any language having an English abstract were included in the first step of the search. We used the following words and terms, including: "Pharmaceutical cocrystal", "Co-crystal method of preparation", "Coformers used in preparation of co-crystal**",** and "assessment of cocrystal". Inclusion criteria in the present study were the studies assessing the cocrystal, coformers, method of preparation of cocrystal, and assessment of cocrystal, but the papers with insufficient data, the abstract without full text, in conformity between methods and results, the inappropriate explanation of the findings were excluded from this review.

Coformers used in the preparation of co-crystal

Excipients that are included in the Inactive Ingredient Database (IID) can be used as coformers with less thorough regulatory evaluation because their safety in a given dosage for a given mode of administration and dosage form may already be known. The choice of coformer for higher-dose medications can be difficult because a comparatively bigger quantity of coformer is needed, which may go beyond the IID limit. For instance, patients older than 15 y should take 400 mg to 1200 mg of carbamazepine as an immediate-release tablet (marketed as Tegretol® in the United States). Considering a stoichiometric ratio of 1:1, The equimolar amounts of Saccharin (SAC), urea, or Nicotinamide (NCT) as coformers would be 930.4 mg, 305.0 mg, or 620.3 mg, respectively, for a dose of 1200-mg of carbamazepine as coformer in the cocrystal. The greatest dosage needed for SAC and urea is above the IID limit, even though NCT is not specified for the oral route. As a result, approving the commercialization of therapeutic products based on cocrystals and including these coformers would add to the regulatory burden [21].

Co-crystal method of preparation

Cocrystal preparation processes include solid-state grinding; solution reaction crystallization, solvent evaporation, slurry conversion, and hot melt extrusion have all been extensively reported to date. It is still necessary to choose a suitable co-crystallization method empirically. The most common cocrystal production techniques shown in fig. 2 and 3 can be divided into solution-based approaches and solid-based methods [22].

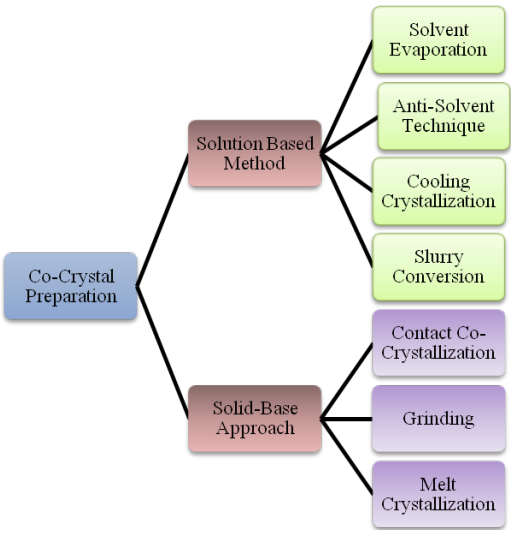

Fig. 2: Illustration of different methods to form co-crystals [22]

Solution-based techniques

The optimal conditions for these reactions, which involve ternary phases in solution, are when the cocrystal is supersaturated and the reactants are either saturated or under-saturated. Although supersaturation of the cocrystal in solution was a crucial factor in co-crystallization, the concentrations of API and coformers may be adjusted. Establishing a phase diagram that details the requirements for thermodynamic stability is necessary to direct the formation of cocrystals. This diagram may assure that the cocrystal stays in the thermodynamically stable area and stop pure reactants from crystallizing. The solubility of the reactants has a major role in determining where thermodynamically stable cocrystal phase zones are found. When the reactants are in a saturated or unsaturated state, the solubilities of the reactants exhibit the ternary phase diagrams, which demonstrate how to supersaturate cocrystals [23].

Solvent evaporation technique

The popular technique for creating cocrystals is solvent evaporation, which is often utilized to create excellent single-crystal cocrystals appropriate for single-crystal X-ray diffraction structural investigation. In this method, the cocrystal is created using this technique by completely dissolving the cocrystal components in an adequate solvent at an appropriate stoichiometric ratio [24]. The choice of solvent affects co-crystallization and could have an impact on the solubility of the reactants. The components of a cocrystal should be uniformly soluble in a particular solvent. The less soluble component precipitates preferentially when two incongruently soluble components co-crystallize, resulting in a solid blend of cocrystal and cocrystal components or the inability to form cocrystals. This approach has been successfully used to produce a large number of cocrystals [25-27].

Antisolvent technique

Antisolvent crystallization, which is carried out in semi-batch or continuous production processes, has been deemed an excellent method to regulate the quality, particle size, and characteristics of cocrystals. For example, Chun *et al.* utilized the antisolvent method to create indomethacin saccharide cocrystals [28-30].

Crystallization cooling

Large-scale and pure crystals may be created utilizing the popular technique of cooling crystallization. In this approach, the crystal properties of distribution size, purity, shape, and crystal polymorphism are determined by the local supersaturation, which is controlled via process variables such as the transformation of mass and heat [31].

Consequently, these variables must be adequately controlled throughout the cocrystal production procedure to assure compliance with various solid-liquid equilibria. The cocrystal's stoichiometry and thermodynamic stability zone at the start and finish temperatures both affect the operating area of the crystallization process. Numerous studies have shown the efficiency of this technology for the scale-up production of cocrystals [32-35].

Co-crystallization in reaction

Reactants with nonstoichiometric concentrations are combined to produce cocrystal supersaturated solutions, which leads to cocrystal precipitation, which works well when the cocrystal components have varied solubilities. The capacity of reactants to reduce the solubility of cocrystals regulates the nucleation and production of cocrystals in this technique [35].

Slurry conversion

The slurry method is used as another method for making cocrystals [36]. The slurry conversion technique involves a phase change that is mediated by a solution, and extra cocrystal components must be added to the solvent. Cocrystal growth is aided by each component's gradual dissolution and creation of a compound throughout the slurry. As cocrystals form, the reactant concentrations decrease, causing undersaturation that permits the cocrystal's constituents to continue dissolving. The cocrystal supersaturation process is controlled by the ternary phase diagram, which also controls the component's functioning temperature and concentration range [37].

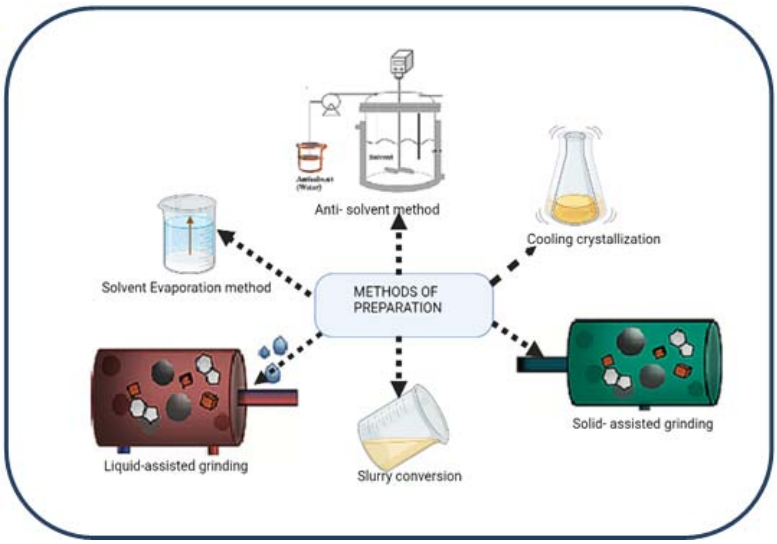

Fig. 3: Methods of Co-crystal formation [23-35]

Solid-based techniques

Direct contact or grinding with higher energy inputs causes crystals to form on their own, making solid-state crystallization procedures efficient and ecologically beneficial for cocrystal creation. They are logical substitutes for solution-based co-crystallization techniques, which might lead to environmental problems because of the heavy solvent use. Solid-based techniques have been utilized to synthesize several medicinal cocrystals [38-41].

Contact co-crystallization

The connecting between the API and coformers may occur on their own after the raw components have been "soft" blended. The creation of the eutectic phase, amorphization, moisture sorption, vapor diffusion of the two solids, and long-range anisotropic molecular movement are among the suggested potential processes for spontaneous crystallization by contact61. Smaller raw material particle sizes, higher temperatures, and greater humidity might promote cocrystal formation [42-45].

Solid-state grinding

Cocrystals are often created utilizing the solid-state grinding technique, which also incorporates liquid-assisted grinding. Without utilizing a solvent, the neat grinding technique uses energy input to create the cocrystal, either manual grinding or mechanical milling. When utilizing liquid as a grinding aid, the cocrystal is created by grinding while utilizing a little quantity of solvent [46].

Neat grinding

Molecular diffusion, the creation of a brief amorphous intermediate, and the production of a eutectic intermediate have all been shown in prior research to be plausible processes of cocrystal synthesis by neat grinding. Grinding creates a movable solid surface, known as grinding molecular diffusion, which causes vaporization or energy transfer. As a result, the tidy grinding process requires solid-state components to have a high vapor pressure so that cocrystals may form on the crystal surface as a result of gas phase diffusion. A new surface for further co-crystallization may be created by removing the formed cocrystal from the reactant surface utilizing the energy provided by grinding [47-51].

Liquid-assisted grinding

The Liquid-assisted Grinding (LAG) method produces cocrystal products having considerable grades and high crystallinity more successfully than conventional grinding. Additionally, such a method also enables rapid cocrystal screening, regardless of the solubility of the donor materials. A significantly little quantity of liquid can also introduce to improve molecular diffusion and accelerate the formation of cocrystals. In the mechanochemical process, the type and amount of liquid are critical variables that influence the creation of various solid products and the size of crystals [52].

Melting crystallization

An additional environmentally friendly method for creating pharmaceutical crystals is melting crystallization. Although this method does not use solvents, this becomes crucial to thoroughly evaluate the chemical and coformers heat stability beforehand. Melatonin and pimelic acid were crystallized together as a cocrystal by Yan *et al.* Melatonin and pimelic acid crystallized when the mixture was between 50 and 70 degrees Celsius in temperature. The physical combination of the chemical and coformer was melted at 160 °C to create the carbamazepine-nicotinamide cocrystal, which was subsequently cooled to room temperature for crystal growth [53].

Table 1: Examples of Co-crystal formulation through various techniques

S. No.	Method	API+Co-former	Reference
1	Solvent Evaporation	Ketoprofen-Malonic Acid	54
2	Solvent Evaporation	Ibuprofen-L-Proline	55
3	Antisolvent Technique	Naproxen-Nicotinamide	56
4	Cooling Crystallization	Fisetin-Caffeine, Nicotinamide	57
5	Slurry Conversion	Ibuprofen-Nicotinamide	58
6	Slurry Conversion	Theophylline–Salicylic Acid	59
7	Solid-State Grinding	Indomethacin-Saccharin	60
8	Liquid Assisted Grinding	Ritonavir-L-Tyrosine	61
9	Melting Crystallization	Melatonin–Pimelic Acid	62
10	Melting Crystallization	Carbamazepine–Nicotinamide	63
11	Neat Grinding	Nicotinamide–Suberic Acid	63

Assessment of co-crystals

Fig. 4: Assessment parameters of cocrystal [65]

Compatibility and study of noncovalent interaction

The compatibility research between chemicals and coformers and intermolecular linking are predicted utilizing Fourier Transform infrared (FTIR) spectroscopy. FT-IR spectroscopy is widely used to study the chemical and physical structure changes in the molecular structure of the substance. The FT-IR spectrum of cocrystals showed relevant changes in the absorption frequencies of the typical functional groups of the pure substances [64]. The prediction of compounds' chemical conformation is often done utilizing this method. Aakeroy *et al.* used FTIR to separate cocrystals from salts by examining the involvement of carboxylic acid in the formation of the hydrogen bond. FTIR is utilized to examine pure chemicals, coformers, physical blends, and cocrystals in the 400–4000 cm-1 range. FTIR investigation can be employed in conjunction with other techniques, like Differential Scanning Calorimetry (DSC) or X-Ray Diffraction (XRD), for cocrystal screening [65-69].

Compatibility and thermal events of cocrystals

Cocrystal formation screening had been done utilizing DSC. The DSC spectrum can be used to screen for the formation of cocrystals if it shows an exothermic peak accompanied by an endothermic peak. These peaks in the physical blend of the constituents suggest the potential for cocrystal formation. Weighed out (1.5-2.5 mg) in aluminum pans, the pure chemical, coformer, physical blend, and cocrystals were then evaluated at heating speeds ranging from 5 to 30 degrees utilizing a corresponding empty pan as a reference. Nitrogen gas, flowing at a rate of 50 ml/min, kept the environment inert. DSC may be utilized to assess endothermic or exothermic behavior, melting point, glass transition temperature, polymorphic character, the heat of fusion, and more [70].

Compatibility and thermal events of cocrystals

To ascertain a solid's physical and chemical properties as a function of time or temperature increase, thermal analysis is used. The temperature of sublimation or decomposition as well as the existence of volatile components, may all be determined utilizing the Thermal Gravimetric Analysis (TGA) technique. TGA analysis helps forecast cocrystal purity, thermal stability, and compatibility. During TGA analysis, the sample mass's weight decreased, which is an indication of volatile component loss or cocrystal disintegration [71].

Structural analysis

For the evaluation of cocrystals, terahertz time-domain spectroscopy (THz-TDS) is an alternate method to Powder X-ray Diffraction (PXRD). Terahertz spectroscopy may be utilized to discriminate between chiral and racemic molecule and supramolecular structures. Theophylline cocrystals with several conformers, including malic acid and tartaric acid, which were present in chiral and racemic forms, were distinguished utilizing terahertz spectroscopy [72]. Solid-state Nuclear Magnetic Resonance Spectroscopy (SSNMR) is used to characterize solid phases that single-crystal X-ray diffraction (SXRD) cannot study. The complexity of the complex was examined using SSNMR by measuring the proton transfer rate. SSNMR is a crucial instrument for identifying salt or cocrystals as a result. By calculating hydrogen bonds and local conformation changes utilized by couplings, SSNMR may also be utilized to assess the cocrystal structure [73].

PXRD is often utilized for cocrystal structure screening and assessment. To assess the structure of cocrystals, the PXRD patterns produced from diffractometers were compared to one another. Cocrystal formation is shown by the differing PXRD patterns of cocrystals compared to their constituents. SXRD is a method used to pinpoint the atomic details of the crystal structure of solids. The main issue with this method is that it is often unable to create a single cocrystal that is acceptable for SXRD investigation. Cocrystal morphology examination and particle size determination were done utilizing a scanning electron microscope. Atoms that contain information about the topography of the sample surface are scanned by high-intensity electron beams [74]. Detailed Process of PXRD fig. 5.

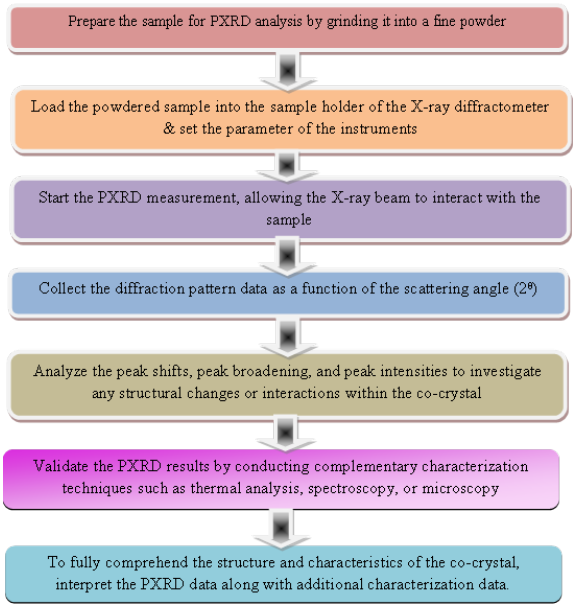

Fig. 5: Procedure of PXRD for evaluation of cocrystal [74]

Dissolution studies

Dissolution experiments are carried out to estimate how effectively the formulation will function *in vivo* and to determine the rate of chemical release over time in the dissolving media**.** The dissolving equipment may be utilized to carry out cocrystal dissolution research. The suitable dissolving solvent is given in the chemical protocol of the relevant pharmacopeia, and here is where the cocrystal dissolution experiments may be carried out. The correct tools, like High-Performance Liquid Chromatography (HPLC) or Ultraviolet (UV) light, can be used to assess the chemical samples in the right amount and at the right time [75].

Solubility studies

The Higuchi and Connors technique for solubility identification may be utilized to evaluate solubility studies. It is possible to assess the solubility of pure chemicals, physical blends, and cocrystals in aqueous or other appropriate media listed in the relevant pharmacopeia. The chemical sample and medium should be placed in a conical flask, which should then be agitated for 24 h at room temperature using a rotary flask shaker. If the drug is light-sensitive, aluminum foil could be placed over the flask to protect the entire sample from light. After 24 h, samples undergo filtering utilizing Whatman filter paper. Aliquots are then properly diluted and analyzed using HPLC or UV light at the right wavelength [76-80].

Stability studies

Stability studies are used to offer information on the shelf life of medicinal products in various storage environments. The storage of pharmaceutical goods in glass vials under varying environmental conditions for varying lengths of time is recommended. The samples are then examined for thermal analysis, chemical release analysis, XRD analysis, and FTIR analysis, and the findings are contrasted with those from the stability study [81].

Perspectives and challenges for the future

The physical and chemical characteristics of medicines can be enhanced through crystallization while the pharmacological properties of the API are preserved. The choice of coformers that are suitable for an API is one of the primary challenges in the production of pharmaceutical cocrystals. There are numerous approaches to choosing coformers and screen cocrystals, but each approach has disadvantages. In the creation of cocrystals, stability in the presence of excipients is also a problem; at the moment, this is an unknown field. The scaling up of the manufacture of high-purity cocrystals has certain noticeable drawbacks that make it an unappealing choice for business. Guidelines for the pharmaceutical sector on the patenting of cocrystals were published by the United State Food and Drug Administration (US FDA) in 2011. Cocrystals were categorized by the FDA as a chemical product intermediary, not a novel API, but rather as an "API excipients" molecular complex. However, according to EMA, cocrystals should follow the same rules for documentation as salt. As a result, even if the USFDA and EMA have distinct regulatory philosophies, it does show the rising focus on utilizing pharmaceutical cocrystals as prospective marketable pharmaceuticals. It takes time and effort to develop, screen, and evaluate novel chemical cocrystals; however, as mentioned in other sections. Some researchers have employed knowledge-based methodologies for coformer selection, crystal design, and screening. Pharmaceutical cocrystals can only be anticipated to strengthen their hold on medication development as cocrystal research continues to expand and new chemical products based on it enter the market.

Low medication bioavailability and low aqueous solubility are important obstacles in the development of oral formulations. Among the many methods for overcoming these difficulties, the use of cocrystals has the distinct advantage of maintaining the chemical's pharmacological qualities while gaining the benefits of the coformer's physicochemical features. The main benefit of utilizing cocrystals over salts is that they may be utilized for medications that are either lowly or never ionizable by nature. So, in addition to straightforward formulation techniques, cocrystals have the potential to increase melting point, tablet ability, solubility, stability, bioavailability, and permeability. Since the cocrystal approach has not yet gotten much attention, a combination of knowledge-based and experimental approaches for coformer selection can usher in a new age in cocrystal formation. Medicinal cocrystals are becoming more and more popular in the industry because of their enhanced medicinal advantages and quicker medication development.

CONCLUSION

Co-crystal chemical delivery methods have shown promise for enhancing the solubility, stability, and bioavailability of medicines with low solubility. Chemical substances interact with co-formers to generate co-crystals, which may enhance the physicochemical characteristics of the chemical substances. The usage of co-crystals has drawn noticeable attention from the pharmaceutical sector, and several co-crystal-based therapies have already found commercial success. The co-crystal chemical delivery system provides a variety of benefits over conventional chemical administration methods, including better solubility and bioavailability, lower dose, reduced toxicity, and more stability. Additionally, the creation of co-crystals is a flexible strategy that may be utilized in other chemical classes and customized to the unique needs of different medications. Co-crystal chemical delivery systems have advanced noticeably, but there are still many challenges to be solved before they can fully realize their promise. Co-former selection, scale-up, regulatory restrictions, investigation of different administration methods, and cost-effectiveness are some of these difficulties. In conclusion, the development of co-crystal chemical delivery systems presents medical enterprises with new prospects to address problems related to less soluble pharmaceuticals. To enhance the co-crystal formation process, provide regulatory criteria, investigate the possibility of different administration routes, and guarantee cost-effectiveness, further research and development are required. Co-crystal chemical delivery systems have the ability to revolutionize the medication development and delivery landscape and provide patients with safer and more efficient therapies with sustained effort and innovation.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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