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A REVIEW ON ORAL DRUG DELIVERY FOR THE APPLICATION OF COCRYSTALS

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ABSTRACT

Among various routes, oral delivery has been recognized as the most attractive method, mainly due to its potential for solid formulations with long shelf life, sustained delivery, ease of administration and intensified immune response. In oral drug delivery, many scientific challenges and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level. The field of pharmaceutical cocrystals has reached a tipping point, particularly because cocrystals can improve the physicochemical properties of drugs without compromising their therapeutic benefits. Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the major constraints during the development of new product. Cocrystals are homogenous (single-phase) crystalline structures composed by two or more components in a definite stoichiometric ratio bonded together by non-covalent bonds. Currently, cocrystals provide exciting opportunities in the pharmaceutical industry for the development and manufacturing of new medicines by improving poor physical properties of Active Pharmaceutical Ingredients (APIs) such as processability, solubility, stability and bioavailability.

KEYWORDS: Biolateral, Supramolecular.

INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. Patient expediency and compliance oriented research has resulted in bringing out safer and newer drug delivery systems.[1] Additionally, a large surface area (>300 m2) lined with a viscous mucosal layer covers the way for drug attachment and subsequent absorption. In contrast with other routes, the absorption mechanism of oral drugs is more complex. Oral

drugs need to be soluble in gastric fluid so they can be absorbed in the stomach, the small intestine or the colon. Orally administered drugs can be absorbed in four types of pathways: Transcellular, paracellular, carrier-mediated transcellular and facilitated transport. Among these pathways, the transcellular pathway is the main mechanism. To meet the increasing demand for biopharmaceutical oral products, research has been focused on developing devices for oral delivery. Although still at a nearly stage, recent devices include intestinal patch systems, micro needle capsules and particulate systems.[2] In oral drug delivery, many scientific contests and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level.[3] The most prominent requirements for a drug delivery system to make it novel are, first to deliver a drug at a controlled rate, and second to pass the active entity to the target site for action. Formulation scientists have been used many possible approaches to achieve this challenging novelty in oral drug formulation, either by unifying drug distribution into a carrier system, or by controlling drug release in the blood to reach the designed plasma drug concentration-time profile.[4] With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is a vital element to achieve this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form as term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[5]

Physiological and biological barrier for oral delivery

Oral delivery through organs in the gastrointestinal (GI) tract needs to overcome several complications.

Lumen: A major step in the absorption of an orally administered drug is transfer of the dissolved drug from the GI lumen to the blood. The absorption of an orally administered drug is controlled by several kinetically discrete steps. The drug first must become available for penetration of the mucosa. This release step may involve for a drug administered as a solid, dissolution, binding to other substances present in the GI lumen, and chemical degradation of the drug in the GI lumen.[6,7] The significant issue to recognize is that the transit time for solid dosage forms or undissolved drug solids in the upper gastrointestinal tract (i.e., stomach and small intestine) typically ranges from 2 – 6 hours. Hence, dissolution rates must be adequately rapid to allow the solids to be dissolved within this time window for absorption to take place.[8] The stomach is the most mixing part, and creates a reservoir

that secretes several enzymes, including pepsin, gastric lipase, hydrochloride acid, and the intrinsic factor. The small intestine is the longest part of the GI tract, and the major site for the absorption of nutrients and drugs. The large intestine is the last major portion of the GI tract. Colon is the site of the most abundant microflora, constituted predominantly of anaerobic bacteria. The gastrointestinal enzymes include the luminal enzymes, gut wall/mucosal enzymes, and bacterial enzymes. These enzymes contribute to the presystemic metabolism of drugs. The gut wall/mucosal enzymes are mostly present in the stomach, small intestine, and colon.[9] Before reaching the bloodstream, drugs encounter mainly three organs: the stomach, the small intestine (subdivided in three parts: duodenum, jejunum, and ileum), and the colon. The luminal pH changes from extremely acidic (pH 1.2–3.0) in the stomach to neutral (pH 6.5–8.0) in the intestine, which raises difficulties for drug molecules, mainly peptides, which possess complex functional structures for their biological activity, which are more susceptible to pH changes.[10] The epithelium layer of the intestinal tract is a group of consolidated cells which act as a cover for the GIT and as mucosal immunological defense against the invading pathogens and harmful chemicals. The most common absorptive areas throughout the intestine are the microvilli covered apical surfaces of enterocytes, which are negatively charged. The distance between microvilli is around 25 nm, therefore they inhibit the passage of larger molecules.[11] To overcome these barriers several strategies have been proposed including the reduction of drug particle size, salt formation or prodrug synthesis.[12]

Mucus: Gastrointestinal mucus also has unique dynamic, physiochemical characteristics.[13] Both the intestinal mucosa barrier and the blood-brain barrier have roles in the absorption of nutrients, electrolytes, and water while restricting the entry of toxins and pathogens (e.g., virus and bacteria). The intestinal mucosa barrier limits oral drug absorption into the systemic circulation to prevent reaching the target tissue. If the target organ is the central nervous system (CNS), the drug has to penetrate the blood-brain barrier (BBB). The intestinal mucosa barrier is composed of microvilli at the luminal side followed by an epithelial cell layer.[14] Mucus layer covers the luminal side of the gastrointestinal tract, and the mucus that is composed of glycoproteins is secreted by the goblet cells. A drug molecule has to penetrate the mucus layer with a thickness of 100–150 μm before crossing the epithelial cell layer of the intestinal mucosa barrier. This mucus layer acts as a filter for molecules with molecular weights of 600–800 da.[15] The gastric mucosa is having a range of pH 1-2 to pH7. Moreover, the presence of dynamic semipermeable sticky gastric mucosal barrier is used for the

exchange of gases, water, odorants, hormones and gametes etc. but is typically restrictive to most bacteria, various pathogens, nanoparticles (foreign substance) prior to its interactions with the epithelial surfaces.[16]

Extracellular: The GI tract has a wide variety of proteolytic enzymes, commonly considered as extracellular barriers, which are involved in the degradation of peptides and proteins, making the oral delivery of proteins and peptides a thorny issue.[17] Two routes are usually distinguished for transepithelial transport: the paracellular route, which allows the passage of small molecules and ions (< 1.5 nm of radius), and the transcellular pathway, which concerns large molecules and small particles. Tight junctions, located at the apical part of the cells, mainly regulate the paracellular route.[18] Absorption via the paracellular route is typically restricted by the narrow space between adjacent enterocytes and the presence of tight junctions that are implicated in the adherence mechanism between adjacent cells. The paracellular pathway does not rely as much on the lipophilicity and hydrogen bonding capacity of molecules compared with the transcellular pathway as it inherently involves the transport of peptides across the aqueous channels in cell junctions.[19] Most drugs are primarily absorbed via transcellular diffusion, permeating through the epithelial cell membrane. Small hydrophobic molecules can partition across biological membranes via a concentration gradient. Hydrophilic molecules generally require some sort of selective transport system to cross the lipid bilayer.[20] For crossing via transcelluar pathways of the intestinal mucosa, the drug molecules have to partition into the cell membranes at the apical side (the mucosa layer) followed by entering the intracellular space after escaping from the membranes due to the concentration gradient. While residing in the intracellular space, the molecule partitions into cell membranes at the basolateral side (blood side) followed by entrance into the blood in the systemic circulation.[21]

Modified release drug delivery system

The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration.[22] Modified release dosage forms are not only able to maintain therapeutic levels of drug with narrow fluctuations but they also make it possible to reduce the frequency of drug administration. A modified-release dosage form is defined “as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or

convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms.[23]

Advantages of modified release drug delivery system

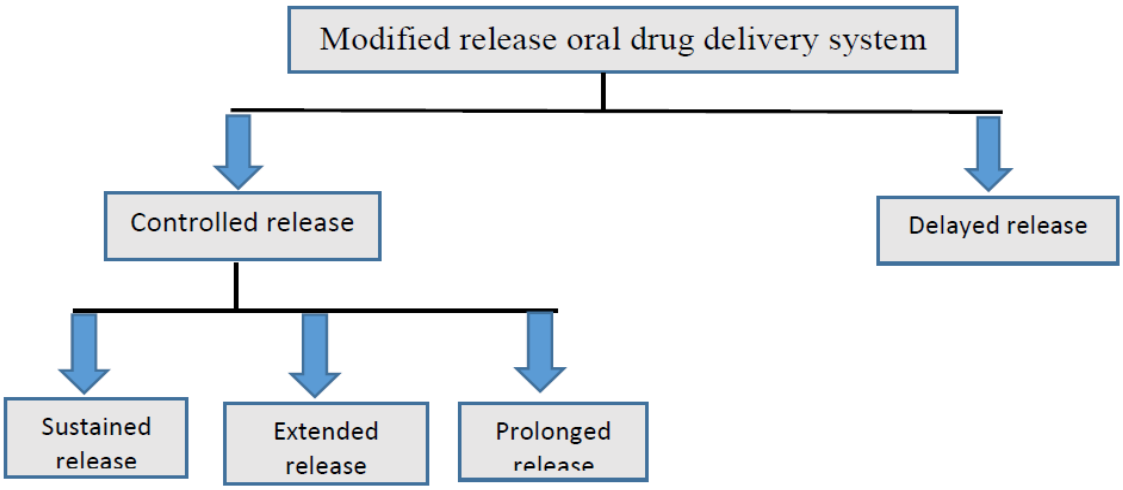
- Reduced dosing frequency
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Uniform release of drug.[24]

Disadvantages of modified release drug delivery system

- Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
- Poor in vitro – in vivo correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.[25]

Classification

Modified release oral drug delivery system may be classified as



Controlled release: The term controlled release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. Also included in this term are systems that provide control over movement of dosage form through the GI tract and / or deliver the drug to a specific area within the GI tract for either local or systemic effect.[27]

The controlled release system divided into following major classes based on release pattern.

- ❖ Rate pre-programmed drug delivery system.
- ❖ Activated modulated drug delivery system.
- ❖ Feedback regulated drug delivery system.
- ❖ Site targeting drug delivery system.

- ❖ **Rate pre-programmed drug delivery system:** In this, the release of drug molecule from the delivery system is pre-planned with particular flow rate profile of medicine. The system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system.
  - Polymer membrane permeation controlled system.
  - Polymer matrix diffusion-controlled system.
  - Micro reservoir partition controlled system.

- ❖ **Activated modulated drug delivery system:** In this, the release of drugs from the delivery system is controlled or activated by the some physical, chemical and biological process or by any supplied external energy source. Drug release controlled by the energy input or any applied process. This activation process can be classified into the following categories.
  - Activation by physical process.
  - Activation by chemical process.
  - Activation by biochemical means.
  - Enzymatic activated system.[28]

- ❖ **Feedback regulated drug delivery system:** In this, a physiological response activates the release of drugs from the carrier. A triggering agent activates the process of release of the drug, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is synchronized by the concentration of a triggering agent that is

detected by a sensor used in the feedback-regulated drug delivery system. Feedback regulated drug delivery system are divided into three part.

❖ **Site targeting drug delivery system:** Delivery of drugs to the targeted site (tissue) is complex, and it is consists of multiple steps of diffusion and partitioning. It is an uncontrolled release of drugs from the drug delivery system, but the path of drug release should be in control. To get read of uncontrolled drug release, drug delivery system should be site targeting specific. It is divided into three parts.

- First order targeting.
- Second order targeting.
- Third order targeting.[29]

Factor influencing the Design and Performance of controlled drug delivery system

❖ **Biopharmaceutic characteristic of the drug.**

- Molecular weight of the drug. Drug stability
- Aqueous solubility of the drug.
- Apparent partition coefficient.
- Drug pKa and ionization physiological PH.
- Drug stability.

❖ **Pharmacokinetic characteristic of the drug**.

- Absorption rate.
- Elimination half-life.
- Rate of metabolism.

❖ **Pharmacodynamic characteristic of the drug.**

- Therapeutic range.
- Therapeutic index.
- Plasma–concentration–response relationship.[30]

Oral Controlled – Release products

❖ Diffusion-controlled products.

❖ Dissolution-controlled products.

❖ Erosion products.

❖ Ion exchange resins.

- Osmotic pump systems.

❖ **Diffusion – Controlled products:** In these systems, there is water- insoluble which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through polymer that forms the controlled release devices. The diffusion can occur through pores in the polymer matrix or by passing between polymer chains. These are broadly divided into two categories-

- Reservoir devices.
- Matrix devices.[31]

❖ **Dissolution-controlled products:** Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer.

- Encapsulation Dissolution Controlled Systems.
- Matrix Dissolution Controlled Systems.[32]

❖ **Erosion products:** It is characterized by a homogeneous dispersion of drug in an erodible matrix.

- Bulk-eroding.
- Surface-eroding Bio erodible systems.

❖ **Ion exchange resins:** It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract.[33]

❖ **Osmotic pump systems:** These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt eg. NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is they created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice.[34]

Delayed release: A delayed release system is that allows at least a two fold reduction in dose frequency as compared to that drug presented as an immediate release form.
Ex: Controlled release, Sustained release.[35]

Cocrystals: According to European Medicine Agency (EMA), cocrystals are "homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)". Cocrystal structure is based in non-covalent interactions between the API and the coformer. The interactions involved are intermolecular interactions, such as van der Waals contact forces, π stacking, hydrogen bonding, electrostatic interaction and halogen bonding between stoichiometric amounts of various molecules.[36] The term "co-crystal" and design rules of hydrogen bonding of an organic co-crystal were first reported by Etter. Co-crystals have regained attention as attractive alternate solid forms for drug development. Cocrystallization with pharmaceutically acceptable compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior.[37]

Screening of cocrystals

Cocrystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio, the solvents, the temperature, the pressure, the crystallization technique, etc.[38] The goal of cocrystal screening is to identify complementary coformers that form a cocrystal with API with enhanced physical and/or mechanical property of an API. It is common for poorly water soluble API to be screened with water-soluble coformers to produce stable cocrystals which allow for higher supersaturation and faster dissolution in water and thus, greater bioavailability.[39] One of the major limitations of current screening methods is that they often lead to crystallization of individual components, are not transferable to larger scale cocrystal formation, require large amount of materials and are time consuming.[40] Coformer selection is the crucial step for designing a cocrystal. During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge Structural Database (CSD), hydrogen bond theories, and many empirical conclusions.

CSD (Cambridge structure database): CSD is valuable tool to study intermolecular interactions in crystals. It can be utilised to identify stable hydrogen bonding motifs, through referring to structural property relationships present in classes of known crystal structures contained in the CSD. A supramolecular library of cocrystal formers has been developed based on the information of CSD, within this library a hierarchy of guest functional groups is classified.[41]

pKa rule: Cocrystals or salts formation can be predicted by proton transfer between acid and base. The formation of salts or cocrystals can be predicted by determining the ΔpKa=[pKa (base)–pKa (acid)]. It is generally accepted that proton transfer will occur from acid to base if the difference in the pKa values is greater than 2 or 3. A smaller ΔpKa value (less than 0) indicates the formation of cocrystals whereas higher value (more than 2 or 3) indicates the formation of salts. ΔpKa rule was validated and quantified by studying 6465 cocrystals from CSD and explained a linear relationship between ΔpKa value and possibility of proton transfer between acid-base pair.[42]

Hydrogen bonding propensity: In cocrystals, drug and coformers interact with each other by noncovalent interaction such as hydrogen bonding, Vander waals forces or p-p stacking interactions. Hydrogen bonding plays an important role and responsible for the formation of cocrystals. Functional groups present on the API would interact with functional groups present on the coformer and they will interact with other. Carboxylic acids, amides and alcohols are the common functional groups of APIs and coformers which are involved in hydrogen bond formation.[43]

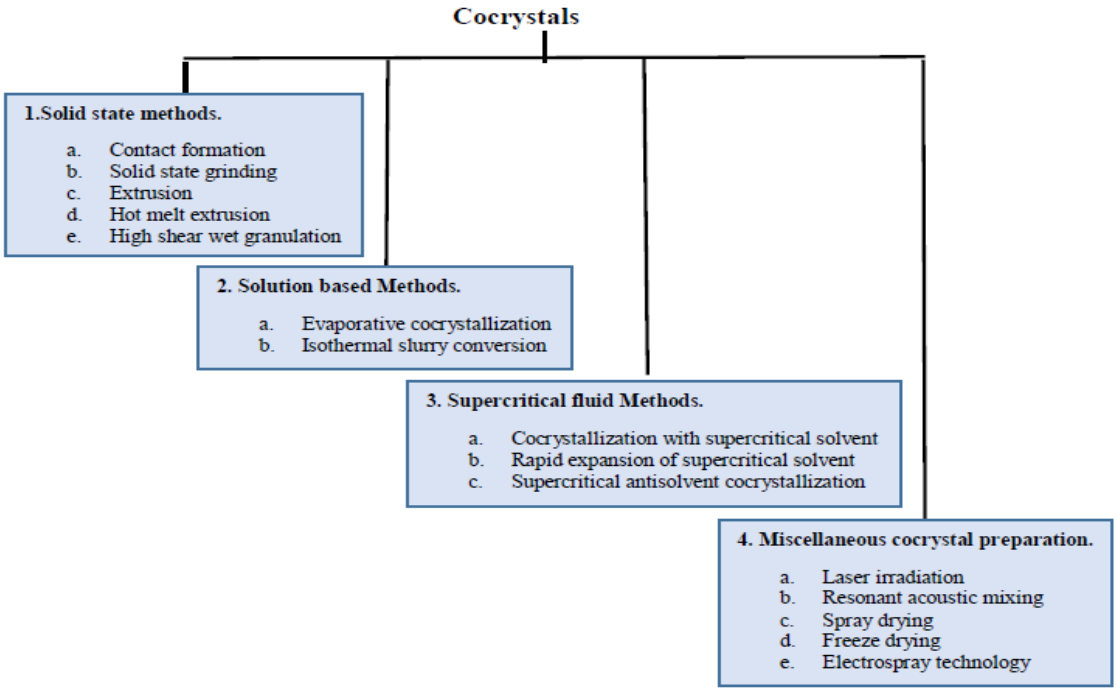
Hansen solubility parameter (HSP): Mohammad MA, et al reported the use of Hansen solubility parameter (HSP) for prediction of cocrystal formation.The concept was originally proposed for predicting polymer solubility in paints by Hansen C.M. The basis of these so-called HSPs is that the total energy of vaporization of a liquid comprising of several individual component forces. These forces arise from (atomic) dispersion forces, (molecular) hydrogen bonding (electron exchange) and (molecular) permanent dipole–permanent dipole forces. The difference in total solubility parameters (Δδt) of the API and conformer is calculated for the purpose of prediction of cocrystal formation.[44]

Binary and ternary phase diagrams: These phase diagrams illustrate the solubility of either API coformer (Binary) or API-coformer-solvent (Ternary). DSC analysis can be employed

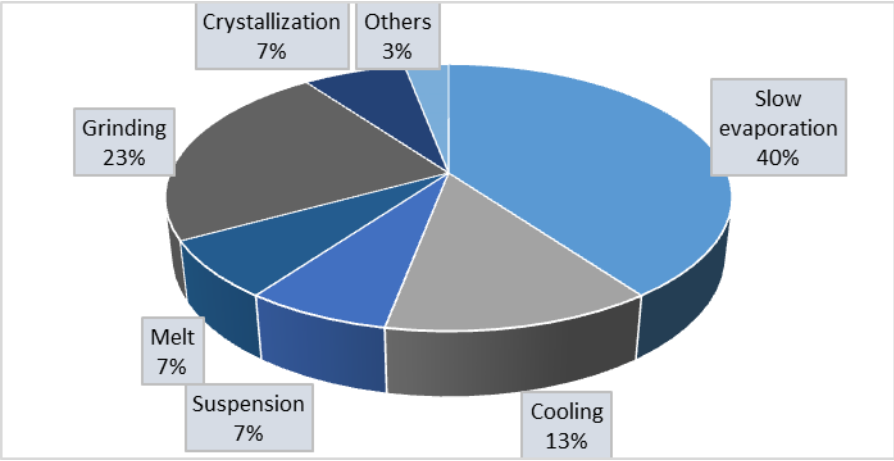
for the construction of binary phase diagram. A 'W' shaped diagram will obtain in case of cocrystal formation rather than a 'V' shaped diagram, which is found when eutectic mixture is formed between the API and coformer. Yamashita et al carried out the coformer screening of salts and co-crystals based on binary phase diagram. Ternary phase diagram (TPD) is a solute-solute-solvent triangular phase diagram that is used for coformer screening in the solution co-crystallization.[45]

Methods of preparation of cocrystals

Co-crystals designed on the principal of the supramolecular synthesis; it provides a powerful approach for proactive discovery of novel pharmaceutical solid phases. The use of hydrogen bonding rules, synthon and graph sets may assist in the design and analysis of cocrystal systems. The co-crystal formation may be rationalized by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallized and how they might interact.[46] Several aspects must be taken into account when choosing the cocrystallization method. For example, API and coformer lability, solubility, stability, susceptibility to form polymorphs, solvates, or amorphous are some of the aspects to consider.[36] With the advancement in drug development, various methods are being used for the preparation of multicomponent solid forms such as cocrystals, cosolvates, coamorphous, polymorphs, hydrates/salts, and eutectics. Solvent selection, API and coformers are the important parameters for such preparations. The various kinds of methods that are most commonly used are:[47]



Cocrystals are synthesized by a wide variety of methods .The figure shows the shares of different methods of cocrystal synthesis among those reported in the literature. As seen from figure, cocrystals are most commonly synthesized by slow evaporation from solution. However, this method does not meet the green technology criterion because of the high solvent consumption. Traditional methods of synthesis of cocrystals from solution are fairly time and labor consuming and scarcely suitable for screening, as screening approaches envision rapid synthesis and analysis of series of samples.[48]

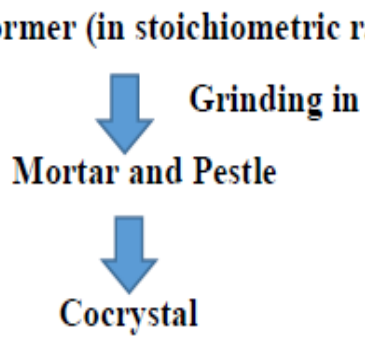


The enhancement of physical property is of a special concern to the pharmaceuticals as the mainstreams of medicines are delivered in solid forms. Physical properties of the solids in pharmaceutical drug product directly affect the processing, delivery, and, eventually, functioning of the drug product. A brief overview of the various methods documented for cocrystal production including their advantages and limitations.

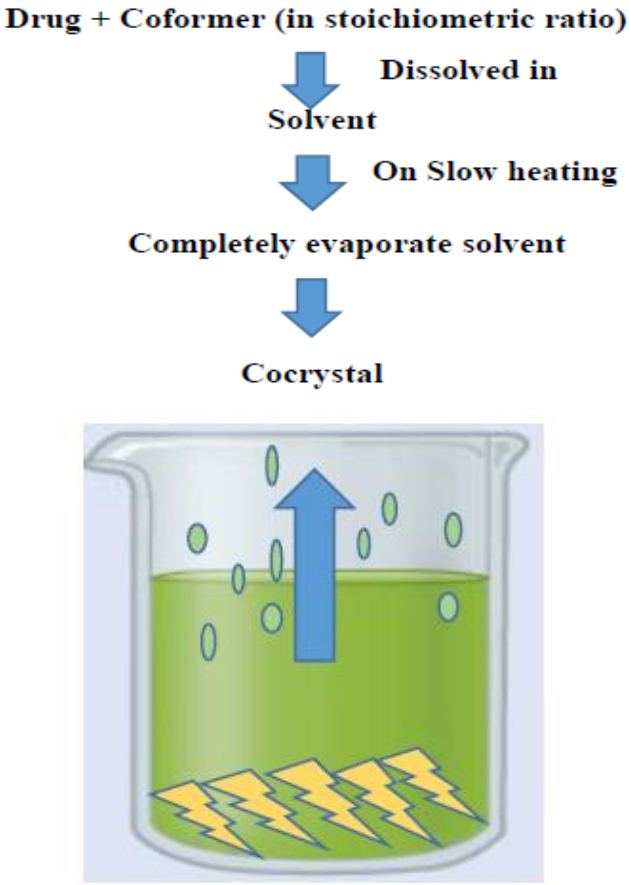
Method	**Advantages**	**Disadvantages**
Solvent methods	High throughput screening method High purity cocrystals Extensive choice of drug and conformer Online process supervising	Use of organic solvents Possible significant difference in the solubility Risk of solvates formation Time-consuming Difficult to scale-up
Neat grinding	Solvent-free process Good purity cocrystals Extensive choice of drug and coformer	Difficult to scale-up Low practical yield Energetically inefficient
Spray drying technique	Continuous and single-step method High purity cocrystals Possible addition of inert or polymers matrix	Use of organic solvents Several process parameters to optimize Several process parameters to optimize
Freeze-drying	Relative more yield Easy to scale-up	Requirement of solvent Lengthy process

Solvent drop grinding	A broad range of drug-coformer pairs High-purity cocrystals	Scale-up problems Chances of solvates formation
High shear wet granulation	Product obtained as granules Ease of scale-up	Use of solvent -Low cocrystal purity
Hot melt extrusion technique	The continuous and simple method Solvent-free green method High purity cocrystals Ease of scale-up	-Expensive due to equipment cost Not useful for thermolabile drugs[49,50]

Solid-State grinding technique or neat grinding: Neat grinding, also called dry grinding or solid state grinding, consist in mixing stoichiometric cocrystal components together in solid state and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. Several mechanisms seem to be involved on cocrystals formation by grinding, in which three are considered essential: molecular diffusion, eutectic formation and cocrystallization mediated by an amorphous phase.[47]



Solvent evaporation technique or evaporative cocrystallization: This is the most commonly used technique for generating co-crystal. The materials (API and coformer) are dissolved in a common solvent with a suitable stoichiometric ratio and completely evaporate. During evaporation, the solution of the molecules undergoes changes, with the creation of hydrogen bonds between different functional groups, thus producing a thermodynamically favored product.[37]



Hot melt extrusion: Hot melt extrusion (HME) is an emerging process employed for the synthesis of high quality pharmaceutical cocrystals. HME is a process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. It is believed that extrusion offers highly intensive mixing, shear and close material packing that improves surface contact between drug-coformer blends leading to the formation of cocrystals without using any solvents.[51]

Slurry crystallization: Slurry crystallization is simple process which includes the addition of crystallization solvent in the components i.e. API along with its acceptable former. The

selection of this process is mainly depends upon the physical stability of the crystallization solution to co crystals and its solid former.[52]

Cooling crystallization: Another solution method called cooling crystallisation involves varying the temperature of the crystallisation system. First, large amounts of reactants and solvent are mixed in a reactor typically a jacketed vessel, and then the system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step. Cocrystals will precipitate when solution becomes supersaturated with respect to cocrystal as the temperature drops down.[53]

Advantages of cocrystals

- Cocrystals having advantages like stable crystalline form (as compared to amorphous solids).
- The only solid form that is designable via crystal engineering patentable expending IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products.[54]

Limitations

- The optimum temperature range should be known for solid‑state grinding method because excessive heating may cause accidental phase transition, conglomerate crystallization or polymorphism.
- Phase separation of co‑crystals into individual component up on storage at certain relative humidity condition also a concern for its applicability.[55]

Applications of cocrystals

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization.[56]

Physicochemical properties of cocrystals

Physicochemical properties of cocrystals are a combination of individual properties of both drug and cocrystal former. For most of the properties of cocrystals, when quantified, has a value that lies between conformer and pure drug.[57]

Melting point: The melting point is a fundamental physical property, which is determined by the temperature at which the solid phase is at equilibrium with the liquid phase. Since melting point is a thermodynamic process where the free energy of transition is equal to zero, the value is determined by the ratio of change in the enthalpy of fusion over the change in the entropy of fusion.[58]

Solubility: As solubility is complementary of dissolution, if cocrystal solubility is increased in comparison to API, intrinsic dissolution is also improved for cocrystals in comparison to pure drug and vice versa. The prediction of this can be done by calculation based on degree of ionization and dissociation equillibria of cocrystals.[59]

Stability: Stability is a very important parameter when evaluating the properties of a pharmaceutical cocrystal. Usually, the stability testing of a newly developed cocrystal includes four aspects: relative humidity stress, thermal stress, chemical stability and solution stability. The relative humidity stress test is used to identify the best storage conditions for the product because the amount of water present in the cocrystal can lead to quality deterioration. Thermal stress and chemical stability are relatively less studied areas about cocrystal properties. Meanwhile, chemical stability of cocrystals is important when developing of these materials.[60]

Intrinsic dissolution: Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, e.g. pH, ionic strength and counter-ions. The sample used in the intrinsic dissolution test is pressed into a disk or pellet, which should be no form change upon pressing and the disk, needs to remain intact during the experiment.[61]

Bioavailability: Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is one of the major challenges in development of formulations, with help of cocrystallization one can enhance or improve the bioavailability of drug. Many researchers has been enhanced the bioavailability of different drug conversion in cocrystals form.[62]

Milestones in the area of cocrystal research

Cocrystals' history begins in 1844 with Friedrich Wohler and the discovery of the first cocrystal, quinhydrone, during the study of quinones.[63] Recent developments suggest that the field of pharmaceutical cocrystals has many fruits to bear, not least in finding new crystal forms, and the potential IP that might accompany such discoveries. There is also a developing understanding of how cocrystals behave in physiological environments and particularly how cocrystallisation could be applied to alternative routes of delivery.[64]

Year	Milestone
1844	Discovery of the first cocrystal by F. Wöhler involving benzoquinone and hydroquinone (termed as quinhydrone)
1963	Principal use of the word "cocrystal" by W.R. Lawton and E.F. Lopez for crystalline complexes involving organic amines and bisphenol
1974– 91	Several drug–drug molecular complexes (cocrystals) involving antipyrene and salicylic acid, theophylline and phenobarbital, pyrimidine and barbituric acid, and sulfaproxyline and caffeine, etc
1990	"Rules" of hydrogen bonding proposed by M.C. Etter are useful for predicting hydrogen-bond patterns in organic crystals (including cocrystals)
1995	Introduction by G.R. Desiraju of the concept of supramolecular synthons in crystal engineering. This has had profound impact on the design of cocrystals
2004	Seminal feature article by Ö. Almarsson and M.J. Zaworotko in Chemical Communications: Formal beginning of the subject of pharmaceutical cocrystals
2005	An article by M.J. Zaworotko and coworkers that raised, for the first time, the question: are cocrystals less or more prone to polymorphism?
2007	A comprehensive review by A. V. Trask on patentability aspects of pharmaceutical cocrystals
2009	Indo-US Workshop on pharmaceutical cocrystals and polymorphs
2011	US-FDA's guidance on regulatory classification of cocrystals
2014	EMA's reflection paper on the use of cocrystals in medicinal products
2015	Entresto: first marketed cocrystal post US-FDA's guidance (2011) on cocrystals that consist of disodium valsartan and monosodium sacubitril. The drug was launched by Novartis for the treatment of chronic heart failure
2016	US-FDA's revised guidance on cocrystals, which eases the regulatory burden of pharmaceutical cocrystals
2018	The United States Food and Drug Administration (FDA) released guidance for industry on the subject of regulatory classification of pharmaceutical cocrystals.

[65,66]

Cocrystals in clinical development and market

Over the past decade, Pharmaceutical co-crystals have seen enormous growth and a large number of research papers and patents have been filed all over the world and till date, a number of patents related to co-crystals and multi-drug co-crystals have been approved. Some of the recently approved pharmaceutical cocrystal formulations are listed.

Summary of pharmaceutical cocrystal products with current status.			
Pharmaceutical cocrystal	**Components**	**Status**	**Indication**
Beta-Chlor®	Chloral hydrate—betaine	Approved by FDA(1963)	Sedation
Depakote®	Valporic acid--valporate sodium	Approved by FDA(1983)	Epilepsy
Cafcit®	Caffeine--citric acid	Approved by FDA(1999)	Infantile apnoea
Lexapro®	Escitalopram oxalate--Oxalic acid	Approved by FDA(2002)	Depression
Suglat®	Ipragliflozin--L-proline	Approved by FDA(2014)	Diabetes
Entresto®	Valsartan sodium--sacubitril sodium	Approved by FDA(2015)	Heart failure
Odomzo®	Sonidegib monophosphate--phosphoric acid	Approved by FDA(2015)	Basal cell carcinoma
Steglatro®	Ertugliflozin-- L-pyroglutamic acid	Approved by FDA(2017)	Diabetes
Abilify®	Aripiprazole--fumaric acid	Marketed	Schizophrenia
Prozac®	fFuoxetine hydrochloride	Marketed	Depression
Sporanox®	Itraconazole	Marketed	Antifungal
Depakote®	Valproate sodium --valproic acid	Marketed	Seizure
Viagra®	Sildenafil citrate	Marketed	Atherosclerosis
T121E01F/T121E02F	Zoledronic acid cocrystals	Under Phase -I Clinical trial, Identifier-NCT01721993	Anticancer
TAK-020	TAK-020--gentisic acid	Under Phase-I Clinical trial, Identifier-NCT02723201	Bruton tyrosine kinase inhibitor
CC-31244	Non-nucleoside polymerase inhibitor	Under Phase-IIa Clinical trial, Identifier-NCT0276075	Non-nucleoside polymerase inhibitor
E-58425	Tramadol hydrochloride—celecoxib	Under Phase-III Clinical trial, Identifier-NCT03108482	NSAID

[54,64,66,67,68,69]

CONCLUSION

For a drug with limited solubility that causes an oral bioavailability problem, cocrystal approach can be a solution. The role of cocrystals in modifying the physicochemical properties of pharmaceuticals has been demonstrated with a special emphasis on solubility and dissolution. The cocrystal strategy is especially advantageous for drugs prone to

degradation under harsh acidic or basic conditions or especially for these neutral compounds or those having weakly ionizable groups. Within the last few years, pharmaceutical cocrystals have attracted considerable attention from the pharmaceutical industry and scientific community because they can provide a wider landscape for investigators seeking to improve upon the solubility, dissolution, and bioavailability of poorly soluble drugs. Pharmaceutical cocrystals provide versatile applications in the development of new chemical entities and improvement of products containing already registered APIs. It will also lead to screening of older API's to see new benefits and improvements of existing drugs. Coformer selection is one of the most important and challenging step in cocrystal development. The basic requirement for a coformer is to be pharmaceutically acceptable among the formulations and also classified as generally regarded as safe (GRAS). In above literature various theoretical and experimental approaches are mentioned to overcome the challenging steps of cocrystal screening. Future research will be focused on the scale-up issues and screening methodology of cocrystal to elevate the profile of cocrystals in intellectual and pharmaceutical background. As cocrystals continue to gain interest and prove their value, the range of demonstrated cocrystal application areas continues to expand. It is anticipated that cocrystals will become more and more routine in pharmaceutical development as their benefits continue to be demonstrated and routine routes of manufacturing are proven.

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