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Co-crystallization is the best way to increase the solubility of poorly soluble drugs an overview

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ABSTRACT-

Background: Cocrystal is a supramolecular chemistry idea this is gaining recognition amongstpharmaceutical and chemical scientists, in addition to drug regulatory bodies. Theprimary cause for that is its capacity to manipulate the physicochemical houses oflively medicinal additives. Formulators must maximize the physicochemical homes ofenergeticmedicinaladditivesevenasenhancingthepharmaceuticalproduct.

Main Text

Pharmaceuticalcocrystalsmaybeusedtoenhanceadrug`sessentialphysicochemical characteristics, inclusive of solubility, dissolution, bioavailability, andequilibrium even as retaining its healing efficacy. It's satisfactory in case you are theuse of an unskilled synthesis manner to make medicinal chemicals. The advent ofpolymorphic forms, solvates, hydrates, and salts of cocrystals sooner or later allthrough the synthesis has been suggested inside the literature as an ability problemwith pharmaceutical cocrystal development. For the logical association of cocrystalsanddecidingonconformersforthesynthesis ofmulti-componentcocrystals,strategiesinclusive of hydrogen-bonding criteria, solubility parameters, screening the use of theCSDdatabase,orthermodynamiccapabilitiesmaybeused.

Conclusion: Searching regulatory cocrystal issues and CSD database growth can help one understand the significance of crystal engineering through co-crystallization in the pharmaceutical field. Becauseoftherelevanceofpharmaceuticalcocrystals, pharmaceuticalregulatorygovernmentswithintheUnitedStatesandEuropehavelaunchedsteeringdocumentsthatcanbeusedtosigninpharmaceutical merchandise in the one's areas. We speak about the layout,synthesis, strategic elements, and capabilities of cocrystals in this article, in additionto regulatoryandhighbrow belongingsconcerns.

KEYWORDS-

Cocrystals,BCSclass,FDA,EMA,co-crystallization,CSDdatabase,Physicochemical characteristics

I. Introduction

Theabsorptionofthedrugismainlylimitedby dissolutionandpermeation.Dissolutionof the drug mainly depends on its water solubility medicine. The drug has limitedsolubility. Development of dosage form becomes difficult for drugs with low solubilityin water. Improve solubility there is enough scope when formulating. Development ofdrugsthatarepoorlysolubleinwater.Usingforgedcopperperformsco-crystallizationsignificantly different from other polymorphs forms, hydration, and solvation. Supermolecule Syntax formation is the key mechanism behind the formation of crystals.Mainlyco-crystallizedRequiresproperhydrogenbondformationtoimprovesolubility.

Supermoleculesynthonsarethespatialarrangementofintermolecularinteractionsinwhich homo and heterosynthone are essential for structural aspects of hydrogenbonding. Various chemical compounds have been used as co-crystalline compoundsin which the carboxylic acid is solid turned out to be more preferred due to its highability to form hydrogen bonds this is structurally important for the formation ofcrystals.[1]

Even if you spend a huge amount of effort and capital Discovery and development ofnew drugs Successful Drugs Candidates often exhibit inadequate physicochemicalproperties.Solubility,stability,dissolutionrate,etc.Solubilitywithbasicpropertiesthataffect bioavailability Dosing of medicine. Over 40% of new chemicals the entity isinsoluble in water, there was one Increasing interest in developing strategies that canbe improved Dissolve drug molecules withoutchanging the molecule Structure

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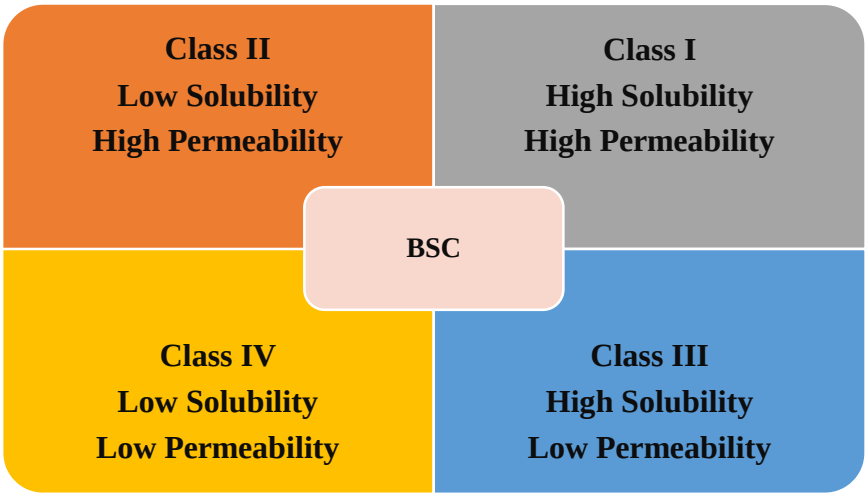
andactivity.[2]
Crystalengineering,whichis"UnderstandingandUnderstandingIntramolecularInteractions Related to Crystal Packing" Use this understanding in the design of newsolids with desirable physical and chemical properties ". Possibility to improve thephysical characteristics of Active Pharmaceutical ingredient (API). Physically Thepropertiesofthecompoundareassignedtothemolecule Sequenceandintramolecularinteractionmolecularinteractionmolecularinteractionmolecule.[3]

There are four classes of drugs according to this classification, viz Class 1: highsolubility–highpermeability,Class2:low solubility–highpermeability,Class3:highsolubility – low permeability, and Class 4: low solubility – low permeability. Several researchers have dedicated their efforts to designing and preparing pharmaceutical co-crystals that can improve the solubility of class 2 and class 4 drugs. In general drug development, the co- crystal approach has achieved relative success wherein several drugs now have improved physicochemical properties and are currently approved by the US Food and Drug Administration (FDA) as pharmaceutical co-crystals.[4,5]



Figno1:BCSclassification

TECHNIQUESOFCO-CRYSTALLIZATION-

Co-crystallizationcanbeachievedbydifferentsolidbasesandsolvent-basedtechniques with good efficiency. The selection of technique mostly depends on thecompatibilityofdrugandco-crystalwiththetechniqueandsubsequentresultstargeted.[6]

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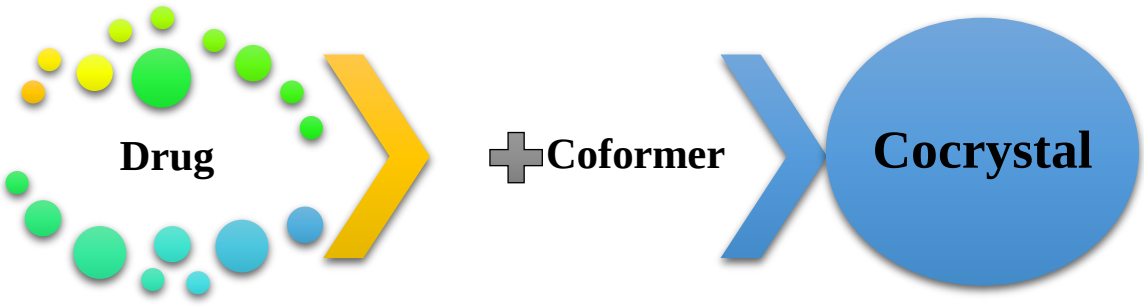

Fig no 2: Cocrystals

Table1:Techniquesofco-crystalpreparation

Sr.no	Techniqueof Co-crystallization	Description	Reference
1.	Neatgrinding	During this process, the medication and co-crystalsare ground together for a predetermined amount oftime.Toachievecrystallisationinalaboratory setting,precisegrindingmaybeused.	[7]
2.	Liquid assistedgrinding	To maximise the potential of co-crystallization, drugand co-former are ground while liquid medium isadded dropwise. The effectiveness and safety of thechosensolvent arekeyconsiderations.	[8]
3.	Extrusion	A high shear rate is used in the hot-melt extrusiontechnique, which causes agglomerates to developwhenco-crystallizationoccurs.	[9]
4.	Cooling co-crystallization	Drugs and conformers crystallise in conjunction viaa cooling-related mechanism. This is a significantsolvent-basedmethodfor co crystalgrowth.	[10]
5.	Evaporative co-crystallization	The fundamental mechanism underlyingcrystallisationistheevaporationofsolventfromthedrug and conformers.	[11]
6.	Reactionco-	Co-crystallizationtakesplaceduringprecipitation	[12]

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	crystallization		
7.	Supercritical fluidtechnology	Useofsupercriticalfluidforco-crystallization	[13]

Main Text

Methods of preparation of co-crystals-

The preparation of co-crystals can be undertaken by several different methods such as neat grinding, solvent drop grinding/liquid assisted grinding, slurring, a solvent evaporation method, anti-solvent addition, supercritical fluid technique, hot-melt extrusion, Sono- crystallization method, spray drying method, laser irradiation, cooling co-crystallization method, high throughput co-crystallization. [14]

Grinding:

The API and co-former additives may be co-crystallized with the aid of using pulverizing without addition of solvent termed as neat grinding or with few drops of solvent termed as solvent-drop grinding or liquid-assisted grinding. Here the substances are blended, pressed and smashed the use of mortar and pestle in laboratories wherein in case of industries, we are able to pulverize in mill. This technique offers particle length lower but if there have to stand up an incidence of co-crystallization those have grew to become out to be a viable method for Solid State grinding along liquid State grinding. [15]

The mechanism worried right here is the low molecular weight additives diffuse without difficulty into the API crystal lattice that could bring about formation of intermediate stages along with eutectic or amorphous section that would in addition results in formation of co- crystal. Inability to form end result of co-crystals with the aid of using grinding is probably due to a powerlessness to provide affordable co-crystal arrangement.[16]

Nowadays a current method of including few drops of solvent to modern-day grinding method has been proven to decorate the kinetics and facilitate co-crystal formation and as cause accelerated solid-country grinding as a technique for co-crystal formation.[17]

Solvent Evaporation-

Solvent evaporation is the maximum ordinary approach withinside the crystallization process. It is likewise a essential method in making ready industrial scale pharmaceutical co-crystals to a restricted extent, in mild of the accessibility of answer crystallization device in pharmaceutical production plants. In this method, each API and co-former are combined with the specified solvent sequentially and evaporatedtotally. During this evaporation process, the molecules withinside the answer are required to shape hydrogen Bonds. The solvent is chosen in this sort of manner that each the API and co-former must display comparable solubility in it. If now no longer then one with least solubility than every other will precipitate out. One of the principle drawbacks of this approach is that it desires extra amount of solvent. [18,19]

Anti-solvent addition-

It's a combination of API and co-former precipitation. Any substance that cannot dissolve is known as an anti-solvent, and water is one of the most common anti- solvents. Let's have a look at how chitosan was employed to create API co-crystals. Chitosan was soaked in glacial acetic acid to make the conformer solution, or chitosan solution. A weighed amount of the drug was disseminated in chitosan solution using a high dispersion homogenizer. The resulting dispersion was combined with distilled water or sodium citrate solution to precipitate chitosan on the medicine.[20,21]

High throughput co-crystallization-

High-throughput screening become at one time a prime technique for locating new co- crystals. Sadly, a level required for the High-throughput screening is luxurious to obtain. The capital undertaking on High-throughput screening become defended in early time of pharmaceutical co-crystal studies whilst the technology had now no longer been very a lot created to manipulate co-crystal screening. Consequently, the opportunity of locating every other co-crystal is improved statistically with the aid of using doing big quantity of experiments. High-throughput stays a treasured device to pharmaceutical enterprise on the present. In any case, it's going to lose its intrigue whilst the Science regarding co-crystallization is more and more developed. Rather, co-crystal layout using the supramolecular synthon and retrosynthetic

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technique is relied upon to grow. In this technique, a crystal, likewise named supra-molecule, is gathered from molecules thru specific intermolecular interactions directed with the aid of using each chemical and geometric houses of the atoms. The eventual destiny of co-crystallization studies will basically earnings with the aid of using the invention of recent synthons, that are structural gadgets for getting ready a crystal. At the factor whilst the potential in crystal shape layout and prediction improves, the High- throughput technique could be gradually unimportant. With mixed high-throughput screening strategies the velocity and efficacy has been substantially elevated in looking new pharmaceutical co-crystals without concerning the formation of co- crystals.[22, 23]

Ultrasound assisted co-crystallization-

In order to incite nucleation in solution and co-crystallize tiny compounds, ultrasound has been widely used. There are a few advantages to ultrasonic-assisted co- crystallization over traditional solution crystallisation. The mechanical energy released by ultrasonic wave passage causes primary nucleation at lower supersaturation levels, reducing enlistment time and metastable zone width. Ultrasound can successfully begin crystallisation from solution, which is difficult to do with traditional solution crystallisation studies.[24,25]

1. Hot melt extrusion:

Co-crystallization method utilising warmness is a singular method to border a co- crystal. It has some factors of hobby contrasted with solvent evaporation method, that is it needn`t hassle with an natural solvent and may be applied without drug and co- former solubility willpower that is a time taking process. Moreover, this method is majorly relying up on thermodynamic balance of components.

Hot-soften extrusion (HME) method is a method that consolidated co-crystal improvement and drug formulation process, show a greater truthful technique to manufacture a drug product, consist of drug and co-former, but moreover an inert matrix. The warmness of HME method is about for precise temperature in this kind of manner that simplest matrix is melted. Co-crystal improvement utilising HME method has nearly equal to device with liquid helping grinding method, wherein a catalyzing agent to enhance co-crystal association performed with the aid of using softened/melted framework as opposed to solvent and the affordable matrices for HME method need to have a following characteristic.[26,27]

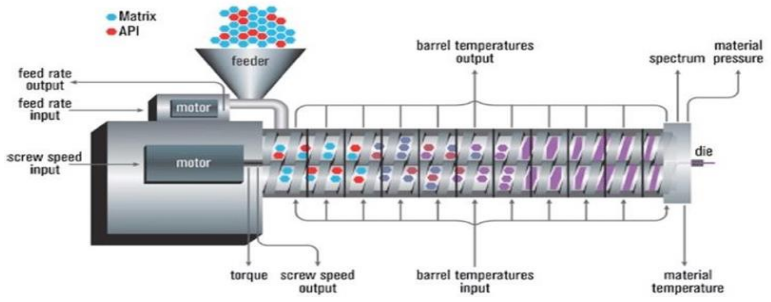

Fig no 3: Schematic representation of a typical HME instrument

Spray drying method:

Spray drying is a quick and continuous method for producing dry powder from a solution or suspension using a heated air stream. Co crystallization using a spray drying technique may be used as an optionally available approach for drug-conformer incongruent dissolvability frameworks when natural co-crystals cannot be formed using a solvent evaporation strategy. Carbamazepine-glutaric acid, theophylline-nicotinamide, urea-succinic acid, and caffeine-glutaric acid co-crystals are examples of incongruent frameworks; these additives cannot produce a natural co-crystal via solvent evaporation, but they can effectively shape a natural co-crystal when spray drying is used.[28,29]

EVALUATION OF CO-CRYSTAL –

Saturation solubility

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To evaluate solubility, an excess quantity of pure drug and cocrystals were dissolved in the 10 ml vials containing drug. The vials were stirred on a rotary shaker for 24 hours to allow for equilibration. After 24 hours, the samples were filtered, diluted with distilled water, and examined using a UV Spectrophotometer at specific wavelength.[30]

Determination of melting point

Melting point of the compounds were determined using digital melting point apparatus.[31]

Drug content-

The co-crystal powder equating to 10 mg of medication was precisely weighed and dissolved in a 10 ml volumetric flask, with the volume adjusted with phosphate buffer pH 6.8. The resultant solution was filtered, diluted appropriately, and its absorbance was measured at Specific wavelength.[32]

IR spectroscopy-

The putative interaction between drug and coformers was investigated using infrared spectroscopy. The samples were combined with potassium bromide and compacted into discs before being scanned with a IR Spectrophotometer.[33,34]

Differential scanning calorimetry (DSC)-

On the DSC, the thermal behaviour of the drug alone and the cocrystal was determined. Weighed samples were inserted into an aluminium pan before crimping and heated at a rate of 5 °C/min under a nitrogen stream, encompassing a temperature range of 0 to 300 °C. Indium was utilised to calibrate the device, and an empty aluminium pan was used as a reference.[35]

Powder X-ray diffraction-

The silicon sample holders were used to get pure Zinc-finger nucleases (ZFN) and cocrystal diffraction patterns (Bruker D8 Advance Diffractometer). Each sample was put on a goniometer head that was motorised to allow spinning of the sample during data collecting, and the equipment was equipped with a sharp focus X-ray tube.[36]

In vitro dissolution study-

The dissolution of cocrystals was investigated using USP type II equipment. A 60- minute dissolution investigation was conducted in 900 of Gastric pH, at 370.5°C and 50 rpm. The trial employed pure drug plus a cocrystal equal to the amount of drug. After a predetermined time period, 5 mL of samples were removed and examined using a UV spectrophotometer at specific wavelength. [37,38]

Stability study-

For three months, the chosen co-crystals were tested for stability at room temperature, 400°C, 20°C, and 75 percent relative humidity (RH). A 1 gm sample was put in an Inspiron tube in a stability chamber for the duration of the stability period and examined after 30 days, 60 days, and 90 days. Drug content, melting point, solubility, in vitro drug release, and other factors were investigated to determine stability.[39.40]

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Fig no 4: Evaluation of cocrystal

Tableno2.TheregulatorystatusofPharmaceuticalcocrystalsinUS,andEurope

CocrystalParameters	USFDA	EMA	Reference
Definition	Solids are crystallinematerialscomposed of two or more molecules inthesamecrystallattice	Homogenous(single-phase) crystalline structures are madeup of two or more components ina definite stoichiometric ratiowhere the arrangement in thecrystal lattice is not based onionicbonds(aswithsalts)	[41]
Regulatorystatus	Drugproduct intermediate (DPI), notregardedasanewAPI	NewActiveSubstancestatus dependent upon demonstrationofefficacyand/orsafety	[42]
SamenesswithparentAPI	Yes	Dependentupon demonstrationofefficacyand/orsafety	[43]
Coformers	Neutralguest compound(excipient)	Non-activecomponents/ Regents(excipient)	[44]

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Regulatory Consideration	Similar to PolymorphofsameAPI	SimilartosaltsofsameAPI	[45]
Chemical interactions	Nonionic	Nonionic	[46]
US-Drugmasterfiles (DMF)/EMA-Active substancemaster file(ASMF)	NotfeasiblebeingDPI	Canbefiled	[47]
ApplicableGood manufacturing practice(GMP) regulations/guide	cGMPfordrugproduct	PartIIofEUGMPGuide (active substances) and ICH Q7andinrare casesPartI ofEU GMPGuide(finisheddrugproduct)	[48]

APPLICATIONS-

The formation of crystals creates a new crystal structure, completely independent of any of the starting materials. This new crystal structure creates a new set of physical properties that are also unrelated to and unrelated to the physical properties of any of the original materials. Currently, the crystal structure and physical properties of a crystal cannot be predicted from the properties of the raw material. Due to the potential improvements in physical properties, the applications of copper crystals are numerous and continue to grow.[49]

Solubility-

Poor water solubility is a barrier to satisfactory drug delivery and therefore often prevents a drug from being fit for its purpose. Essentially, the crystal will have a different solubility than the initial. starting material because the underlying crystal structure is altered. The change in solubility can be in either direction. Solubility enhancement is desirable as it improves drug bioavailability, but excessive enhancement can be problematic as it can lead to undesirable precipitation of starting material due to the formation of solvent.[50]

Bioavailability-

Release control. Co-crystallization provides an opportunistic approach to tune the physicochemical properties of pharmaceuticals, including solubility and dissolution rate. In particular, depending on the co-crystallizer with the API, the dissolution rate of the API in water or buffer solution may increase or decrease over time. Carbamazepine and cinnamic acid crystals synthesized by solvent evaporation show higher dissolution rates, solubility and, stability in water than carbamazepine.116 Arenas-Garcia et al. produced some acetazolamide (ACZ) crystals with an improved intrinsic dissolution rate compared to pure ACZ in media simulating physiological conditions (HCl 0.01N, pH 2.0) .117 Crystals.[51]

The crystals that can provide the highest dissolution rates are those crystals that exhibit a steady-state in the same medium by initially undergoing a solvent-

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mediated phase transition. Cocrystals also have the ability to reduce the dissolution rate of native APIs.[52]

Multidrug Cocrystals-

Combining multiple Active Pharmaceutical Ingredients (APIs) into a single dose has become a common trend in the apothecary industry. The need to target multiple receptors to effectively treat complex disorders such as HIV/AIDS, cancer, and diabetes, coupled with the growing need to facilitate reductions in drug manufacturing costs, are two reasons. for this growing trend. Salts, neutral complexes, homomorphic systems, and crystals are the systems that have been used to combine multiple APIs into a single delivery system.[53]

Lots of Multidrug crystals (MDCs) have advantages over systems homomorphism in increased stability and compared with the load to the mesopoured and cyclodextrin complexes. Thiparaboina et al. MDCs are defined as "dissociable crystalline solid supramolecular complexes consisting of two or more therapeutically effective components in percentiles in the same crystal lattice, where the components may be similar to each other. mainly through non-ionic interactions and rarely through hybridization (a combination of ionic and non-ionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of molecules. solvate death.[54]

MERITS OF CO-CRYSTALS-

Co- crystals with advantages such as stable crystalline form (compared to amorphous solids), no need to make or break covalent bonds, the theoretical ability of all kinds of API molecules (can be weakly ionized / non-ionized) to form copper crystals, the existence of many potential anti-molecular substances (food additives, preservatives, pharmaceutical excipients ,and other APIs), single solid form can be engineered through an extended patentable IP portfolio and can be manufactured using solid-state synthesis, high yield, green technology with no solvents or by-products.[55]

Factors that play an important role in influencing the physicochemical properties are the properties of the API and the transducer, the nature of their molecular interactions, and the synthesis procedures used. The main advantage of the co-crystal formulation is that it does not alter the pharmacological properties, APIs would benefit from enhancing their physicochemical properties due to the presence of copolymers in thecrystal structure. a component that changes properties. The effect on the physicochemical properties of the API depends on the condensate available. Another unique advantage of crystals over more common salts is that crystals can be fabricated for non-ionizing APIs as well as complex drugs with sensitive functional groups that may not exist in harsh reaction conditions of strong acids or salts.[56]

There are several other key advantages behind the formulation of copper crystals. Cocrystals have the potential to shorten API's drug development time. Shorter development times mean less costs, which is attractive to pharmaceutical companies. Solid-state cocrystal synthesis techniques can be classified as green chemistry because they yield high yields, use no solvents, and have few by-products.[57]

Pharmaceutical crystals have a different structure from their bulk form; could patent existing API cocrystals as a new crystal form. Various formulations of pharmaceutical copper crystals are commercially available, such as Viagra (Pfizer) for the treatment of erectile dysfunction and pulmonary arterial hypertension, Entresto (Novartis) for the treatment of chronic heart failure, and several others are in clinical development. [58]

II. CONCLUSION

The significance of crystal engineering through co-crystallization in the pharmaceutical subject may be understood by searching regulatory cocrystal concerns and CSD database growth. On the only hand, cocrystals are all at once fashioned in the course of processing118- one hundred twenty at the same time as on the different researchers would require the careful choice of cocrystal layout technique as in a few cases, cocrystals are now no longer fashioned as in step with predictions which suggest demanding situations in formulating cocrystals.137 Cocrystals' capacity to flourish favoured physicochemical and biopharmaceutical properties of API to the most efficient volume opening a brand new panorama to Cocrystals of more than one lively substance that may be formulated as constant dose combos for higher healing applications. It will stimulate research of antique APIs to look for new benefits. There is a want to explore the knowledge of co crystallization mechanism, in vivo conduct of cocrystal for higher therapeutics, and different unanswered questions like polymorphic transformation. It is a possibility to seize for patenting new cocrystal kinds of API.

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LIST OF ABBREVIATIONS

SR,NO	LIST OF ABBREVIATIONS	
1	Active Pharmaceutical ingredient	API
2	Food and Drug Administration	FDA
3	Hot-soften extrusion	HME
4	Differential scanning calorimetry	DSC
5	Zinc-finger nucleases	ZFN
6	Relative humidity	RH
7	Drug product intermediate	DPI
8	Acetazolamide	ACZ
9	Multidrug crystals	MDCs
10	Absorbance	Abs
11	Biopharmaceutical classification system	BSC
12	Indian Pharmacopoeia	IP
13	Cambridge Structure Database	CSD
14	Hydrochloric Acid	HCL
15	Gastrointestinal tract	GIT
16	Drug master files	DMF
17	Degree Centigrade	°C
18	Revolutions per minute	rpm
19	United States of Pharmacopoeia	USP
20	Ultra Violet	UV
21	Percent	%
22	Standard	Std
23	European Medicines Agency	EMA

CONFLICTS OF INTEREST-

There are no conflicts of interest and disclosures regarding the manuscript.

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FIGURE LEGEND

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2	Cocrystals	2
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