Review Article

Insight into Concept and Progress on Pharmaceutical Co-Crystals: An Overview

Venkata Deepthi Vemuri[1,*], Srinivas Lankalapalli[2]

[1]Maharajah's College of Pharmacy, Phool Baugh, Vizianagaram, Andhra Pradesh, INDIA.
[2]GITAM Institute of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, INDIA.

ABSTRACT

Pharmaceutical co-crystals have conferred significant recognition in recent past as a new solid form by virtue their capability to modulate physicochemical properties of Active Pharmaceutical Ingredient (API). Nevertheless, pharmaceutical progress of co-crystals could be provocation, the requirement for high-throughput screening methods and the techniques capable of co-crystal production in industrial scale still hamper the co-crystal used by industries. In this review, well ordered overview of pharmaceutical co-crystal is provided, with focus on role of supramolecular chemistry, co-crystal design strategies, preparation methods, physicochemical property studies, mechanism of solubility enhancement, evaluation techniques. In the present commentary, the impact of choosing appropriate process design and formulation on translational challenges has been discussed. Eventually, a short outline of applications and marketed drug products of pharmaceutical co-crystal drug substance is also described.

Key words: Co-crystals, Crystal engineering, Physicochemical properties, Co-crystallization, Translational challenges.

INTRODUCTION

The process of developing a new dosage form from a new chemical entity is a complex process. It involves in strategic and exploratory research in the selection and development of medical product. Whereas the molecule has to pass different stages of development to reach the required criteria. Incomplete information about its properties and pharmaceutical manufacturing capabilities in advance to clinical trials may lead to complex and costly problems at the later stage.[1] Considering these cases improving the existing molecules founds more beneficial than the new molecule. Most of the solid-state Active Pharmaceutical Ingredients (APIs) exist mainly in two morphological structures crystalline or amorphous (Figure 1). Among these crystalline materials are more preferred for product development due to their high stability when compare to the amorphous forms (less stable and leads to re-crystallization over time).[2] Even though crystal forms are stable, reproducible and easily purifiable than other types of solids the major drawback is its low solubility. Amid all the biopharmaceutical properties, solubility remains as main issue for most of the API's.[3] Solubility and dissolution rates are the most important considerations to determine the performance of the drug. Improvement in these aspects without change in the molecular structure is the most challenging aspect for successful development of new product. Currently, many strategies have been adopted for improving the solubility to attain the improvement in their absorption and bioavailability of the drugs, including milling techniques,[4] hot melt extrusion,[5] self-emulsification,[6] solid-dispersion,[7] inclusion-complex[8] liposomal formulations,[9] nanoparticles.[10]

Co-crystallization is one of the alternative ways to solve the problems confined with the physicochemical properties of the

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Correspondence:
Mrs. Venkata Deepthi Vemuri,
Assistant Professor, Maharajah's College of Pharmacy, Phool Baugh, Vizianagaram-535002, Andhra Pradesh, INDIA.
Phone: +91 9032292387
E-mail: deepthichowdary438@gmail.com

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API. Over the last twenty years a number of publications have been shown the significant increase in the use of co-crystal and their possible use in the formulation as an optimization strategy for solubility, dissolution rate, physical stability and bioavailability of API's.[11] This is encouraged by the recent FDA reclassification, from which co-crystals are considered as drug polymorph rather a new API,[12,13] including solvates to ease the regulation burden on manufacturers that work with them.[12,13] Many of co-crystal strategies like solvent change techniques,[14] Solution co-crystallization,[15] thermal methods,[16] ultrasound assisted,[17] grinding methods[18] have been emerged. Previously, many of the case studies and reviews conducted in co-crystals reported, superiority of co-crystallization technology in comparison to other strategies,[19] improvements in manufacturing of drug dosage forms,[20] enhancements in drug properties by bottom-up approach,[21] pharmaceutical co-crystallization techniques,[22] translational development challenges,[23] impact of co-crystals on drug pharmacokinetics,[24] Co-crystallization of neutraceuticals,[25] Vibrational spectroscopic investigations on co-crystallization.[26] Improvement of physicochemical properties of co- crystallization have been well explored.[27]

Supra-molecular chemistry and crystal engineering

The scientific community had some disagreement with co-crystal definitions which were subjected in the past. European medicine agency defined co-crystal as a crystalline homogeneous structure having two or more components arranged in a crystal lattice with a definite stoichiometric ratio (EMA 2015). Co-crystals are formed by intermolecular interactions such as halogen bonding electrostatic interactions, π stacking, hydrogen bonding and Vander walls forces which are non-covalent between API and the co-former.[20,28] Figure 2 shows the schematic formation of co-crystal. Supramolecular synthons, homo-synthons and hetero-synthons[29] refer to structural units within supramolecules which are formed by intermolecular interaction by known synthetic operations.[30] A comparison between FDA and EMA guidelines of Pharmaceutical co-crystals was discussed in Table 1.[31]

Crystal engineering involves breaking and forming non-covalent bonds, rearrangement of molecules within the crystal packing. In turn, it is effective in designing supramolecular synthons[32,33] and ultimately results in co-crystals formation, which may lead to the improvement of physicochemical properties of API without affecting its structure and functions. An acid group of carboxylic acids, alcohol groups and amide groups are the common functional groups involving in supra-molecular synthon formation by H-bonding.[34,35] Co-crystal formation is more favored by hetero-synthons than homo-synthons,[36,37] The intermolecular interactions involved in co-crystal formulations should be non-ionic,[34] with no proton transfer. If the proton transfer is completed

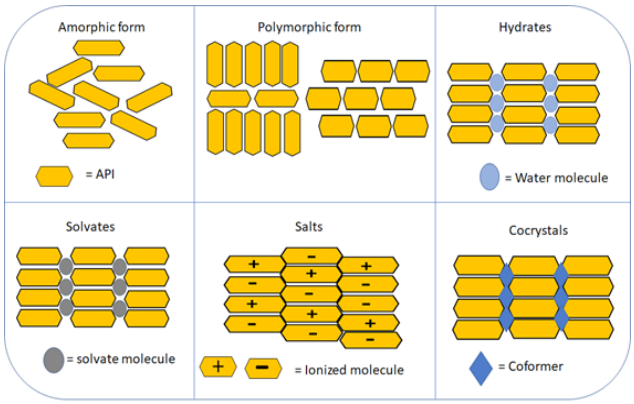

Figure 1: Schematic representation of solid forms classification.

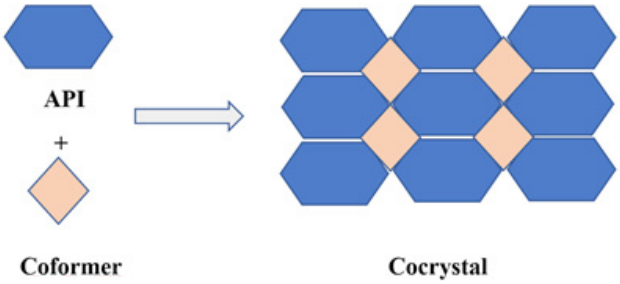

Figure 2: Schematic representation of co-crystal formation.

Table 1: Comparison between FDA and EMA guidelines of Pharmaceutical co-crystals.[31]

Regulatory guidelines	EMA (2015)	FDA (2016)
Regulatory category	Active pharmaceutical ingredient	Polymorph of active pharmaceutical ingredient
Composition	Active pharmaceutical ingredient and co-former in fixed stoichiometric arrangement	Active pharmaceutical ingredient and a food or drug grade co-former
Co-former role	Reagent	Excipient
Interaction in crystal	Non – ionic / non-covalent interaction	Non – ionic / non-covalent interaction
New active substance registration	Possible if shown dissimilar in efficacy/safety	No
Classification	Salt of Active pharmaceutical ingredient.	Polymorph of Active pharmaceutical ingredient.

it leads to salt formation.[38] This proton transfer mainly depends upon the pKa values of the API and co-formers. According to FDA[39] Δ pKa is considered as a threshold for distinguishing between co-crystals and salt. FDA also indicates, the formation of salt will happen in the components having Δ pKa ≥ 1. If the component having Δ pKa < 1 result in co-crystal formation. In addition to FDA indications, others expressed "rule of thumb" states Δ pKa > 2.7-3 units, formation of salt is likely to happen than cocrystal.[40]

Fine-tuning of API properties by using crystal engineering would be beneficial to the pharmaceutical industry. Co-crystals found to be better than salts, polymorphism, solvates and amorphous forms

Effect of co-crystals on physicochemical properties of API

Along with all other aspect's investigations of physicochemical properties plays most important role in developing the new dosage form.[41] These physicochemical properties of the drugs can be adjusted with an increased instability and efficiency of dosage form by using co-crystallization techniques.[42] Schultheiss and Newman gave a review based on these properties and some of the key physicochemical properties are melting point, solubility, stability dissolution bioavailability.[43]

Melting point

Melting point, as it is having a correlation with aqueous solubility and vapour pressure[44] used in purity identification and characterization. Melting point is one of the key factors essential to characterize the polymorphs of a compound (Monotropic or Enterotropic).[45] Many of the researchers stated that the co-crystals provide an excellent opportunity in modifying and fine-tuning the physicochemical properties of the existing molecules.[43,21,46]

A comparison melting point study was done by Staton and Bak using 10 co-crystals with API AMG517 with their respective co-formers, among these all the co-crystals have shown the melting point between the melting points of API and their corresponding co-formers.[21] Linear correlation between the melting points of hexamethylene bisacetamide co-crystals were reported with five different even numbered aliphatic dicarboxylic acid co-formers which are selected with similar structures and different melting points.[46]

Nate Schulthesis, 2009 conducted a survey on 50 cocrystal samples, the majority of them have shown the melting point between that of the API and co-formers.[43] Fleischman, 2003 carried out to investigate on the on four co-crystals with different crystal packing arrangement but same heteromeric O-H…N hydrogen bond. These co-crystals had different melting points showing the impact of crystal packing arrangement on melting point.[47]

Stability

Stability is the most important parameters to be studied during the development of any new molecule the self-life of the molecule mainly depend upon the chemical and physical stabilities (ICHQ1A). The following are the aspects to be considered for stability testing.

Relative humidity (RH) stress

RH stress provides the information about the water content in co-crystals which leads to deterioration of molecules. This in turn helps in determining the best storage condition.[48]

Many of the literature concluded that the co-crystals are stable to moisture under normal storage conditions.[49-52] Dynamic vapour sorption and desorption experiments on co-crystals of Indomethacin saccharin (1:1) showed a very negligible amount of moisture was sorbed by co-crystals with no solid-state transformation.[49] MC Namara conducted repeated sorption/desorption cycles on co-crystals of glutaric acid and 2-(4-(4-choro-2-flurphenoxy) phenyl) pyrimidine -4-caroxamide. The data revealed that the moisture uptake is less the 0.008% and the relative humidity was up to 95%.[50] Bak A showed that AMG517/sorbic acid co-crystals with minimum moisture update 0.7% and with no solid-state transformation with sorption/desorption cycle.[27]

Some of the literature supported with adequate physical stability of co-crystals even in the long-term stability studies concerning for to RH.[52] Trask conducted studies with 6 caffeine co-crystals which were placed at 4 RH conditions (0, 43, 75 and 98% RH). These samples were analyzed after 1, 3, 7 days and 7 weeks. This study reveals using strong acid with caffeine produced the most stable co-crystal whereas weakest acid gave the least stable co-crystal.[53]

Thermal stress

This is the most important parameter used to determine physical and chemical stability.[54,55] Chen prepared co-crystals of a monophosphate salt and phosphoric acid with were exposed to 60°C for 8-weeks and noticed with no degradation.[56]

Chemical stability

These studies were normally conducted using accelerated stability conditions such as 40°C/75% RH and 60°C/75% RH to minimize the chemical degradation of the formulation. Only limited research work was done

on the chemical stability of co-crystals. Chen, 2007, conducted stability studies of co-crystals of monophosphate salt with phosphoric acid using 40°C/75% RH and 60°C/75% RH for 8 weeks and reported to have no detectable degradation.[56] Another study was conducted with co-crystals of 2-(4-(4-chloro-2-fluorphenoxy) phenyl) pyrimidine-4-carbonxamide with glutaric acid using same conditions for 2 months and reported with no detectable degradants by HPLC impurity analysis.[50] Another literature compared the chemical stability of carbamazepine (parent API) with 1:1 carbamazepine saccharin (co-crystals) using temperatures of 5°C, 40°C and 60°C at ambient humidity and elevated RH conditions of 25°C/60% RH and 40°C/75%RH for 2 months. Results revealed with no degradation at different temperatures and similar degradation with second condition.[57] Based on these literatures we notice that the co-crystals may exhibit better chemical stability.

Solution Stability

Solution stability is defined as the ability of co-crystals to stay in solution without converting into crystals.[43] Solution stability along with solubility and dissolution studies play a very important role in understating the nature of co-crystals in releasing media. Trask 2006 along with RH studies, conducted a solution stability test for 2:1 caffeine/oxalic acid co-crystals by preparing slurry with water at ambient temperature for two days and noticed that there is no change in its physical form indicating the stability of co-crystals. In another example the study involved in the screening of twenty carbamazepine co-crystals formed with 18 co-formers which were slurred with water for 20-48 hr. Among these, only seven co-crystals maintained their structure and remains are converted to carbamazepine dihydrate. The Author noted that the high aqueous solubility of co-formers has the chances of structural instability.[58] Solution stability can be obtained by solubility and intrinsic dissolution experiments in aqueous media. MC Namara, 2006 conducted an intrinsic dissolution experiment on co-crystals of 2-[4-(4-Chloro-2Flourphenoxy) Phenyl] Pyrimidine – 4 – Carboxamide with Glutaric acid for 90 min at 37°C using water. Results showed that there is no major conversion to parent molecule, the remaining portion left in the apparatus showed the complete conversion to the parent molecule within 24 hrs under 37°C.[50] Another literature conducted aqueous solubility on 4 co-crystals of Fluoxetine Hcl with Benzoic acid, Fumaric acid and Succinic acid. Among these co-crystals Benzoic and Fumaric acids showed no change in its structure at the end of the experiment. But Succinic acid co-crystals exhibited complete conversion to Fluoxetine Hydrochloride. In this study, the author reported that the Succinic acid is a conformer having highest solubility and it was co-former to dissociate.[59]

Solubility

Solubility is the thermodynamic equilibrium of solute between the liquid phase and solid phase.[60,61] Pharmaceutical co-crystallization is considered to be the most effective way of improving the solubility on which many of the researches have been reported.[3,46,50,59] Ramenar compared three Itraconazol co-crystals with crystalline Itraconazol and reported with high solubility of co-crystals than crystalline form.[62] Shiraki prepared 2 co-crystals, Exemestane/Maleic acid and megestrol acetate/saccharin from organic solutions with different particle sizes. Both the co-crystals showed improvement in dissolution rates at the initial stage when compared to the respective original crystals. Fine particle co-crystals of Megestrol acetate/saccharin showed supersaturated concentration of Megestrol acetate for about 6 folds more than MA within 15 min and 2 folds more within 4 hr. Co-crystals of Exemestane/Maleic acid transformed to parent crystal within 1min in suspension. These co-crystals even larger particles have shown higher dissolution rates[63] Good and Redriguez-Hornedo, 2010 published a theoretical analysis for predicting the co-crystals solubility. Co-crystal eutectic constant (K_{cu}) Plays a major role in the selection synthesis and formulation of co-crystals. K_{cu} values were used to predict the phase behavior, ionization and complexation.[64] Co-crystallization approach for poorly soluble drugs like Carvedilol shown better bioavailability, solubility and dissolution in comparison to other strategies.[19] A NMR crystallographic study on niclosamide co-crystals, reported the improvement of equilibrium solubility of 1:1 niclosamide – thiazole cocrystals 2.8 folds to that of pristine niclosamide.[65]

Mechanism involved in solubility enhancement

Solubility depends mainly on crystal lattice strength and solvent affinity. Co-crystals have the ability to reduce the lattice strength and to enhance the solvent affinity.[66,67] Aqueous solubility of the co-crystals is mainly affected by solvation, leads to an increase in drug hydrophobicity.[68,69] Due to this hydrophobicity, many of the co-crystals of hydrophobic drugs have shown less solubility than that determined using lattice energy.[27,67] Many of the literatures correlated the solubility of co-formers with the solubility of co-crystals.[67,70] This indicates that the nature of co-formers will affect the solvation barrier of co-crystals.

Spring and Parachute effect

Spring and Parachute phenomenon was explained by Guzman, this concept improves the solubility of hydrophobic drugs by using a supersaturation strategy. This mechanism involves in the origination of supersaturated Metastable state and its maintenance.[71] The weak Bonds (Hydrogen bonds) that connects the drug and the co-former in co-crystals[72] are dissociated, which leads to the release of high water-soluble co-former from the crystal lattice of co-crystal to the biological medium. The Hydrophobic drug has been converted to supersaturation state which is having higher energy than its crystalline molecule called spring. This spring will precipitates to clusters immediately. The maintenance of this super saturated stage for a sufficient period is beneficial for improving the solubility Figure 3. Using some of the excipients or compounds which intervene with crystal growth may lead to inhibit the precipitate and maintain spring state this referred to as parachute. This state lasts for a long time in the dissolution medium showing high solubility. This stage transformer follows Ostwald's Law of stages.[63-74] Childs, 2013 prepared 1:1 Danazol/Vanillin co-crystals which results in 1.7 times rise in AUC with simple aqueous suspension. Whereas these co-crystals have shown 10 times rise in AUC when suspended in the aqueous phase containing TPGS and HCP as solubilizes and precipitate inhibitor respectively.[75]

Intrinsic dissolution

Intrinsic dissolution indicates the rate of dissolution of a compound from constant particle size. Intrinsic dissolution rate is one of the best indicators for the *in vivo* performance of most of the co-crystals, which belongs to BCS class II drugs. Only limited numbers of literatures are available on intrinsic dissolution.[50,59,63] M C Namara conducted intrinsic dissolution studies on glutaric acid co-crystals of 2-[4-(4-Chloro-2Flourphenoxy) Phenyl] Pyrimidine – 4 – Carboxamide using water over 90 min. This study was reported to increase in dissolution of co-crystals with 18 times than that of the parent molecule.[50] Another study was conducted on three co-crystals of Fluoxetine HCl and different co-formers, 2:1 Fluoxetine HCl/Succinic acid co-crystals have shown a threefold increase of dissolution over parent molecule, 2 co-crystals which are made up of Benzoic acid and Fumaric acid showed reduced and same dissolution rates respectively with the comparative parent molecule.[59] Shiraki measured intrinsic dissolution on 2 co-crystals. 1:1 Exemestane/Maleic acid showed the same dissolution rate as parent molecule whereas 1:1 Megestrol acetate/saccharin co-crystals showed a 3-4-fold increase in dissolution rate than the parent molecule.[63] More studies should be needed for the exact role of co-crystallisation on the intrinsic dissolution rate.

The melting point of most co-crystals is resulting in the melting points between API and co-former. In most cases, stability was improved resisting hydrate formation was shown in co-crystals. Solubility and dissolution improvement for poorly soluble compounds were achieved by co-crystallization. It was shown that a worthy degree in bioavailability is possible with co-crystals.

Formulation of co-crystals

Design strategy and co-former selection

The design and preparation of pharmaceutical co-crystals is a complex and multistage process, represented schematically in Figure 4. Co-crystal designing can be

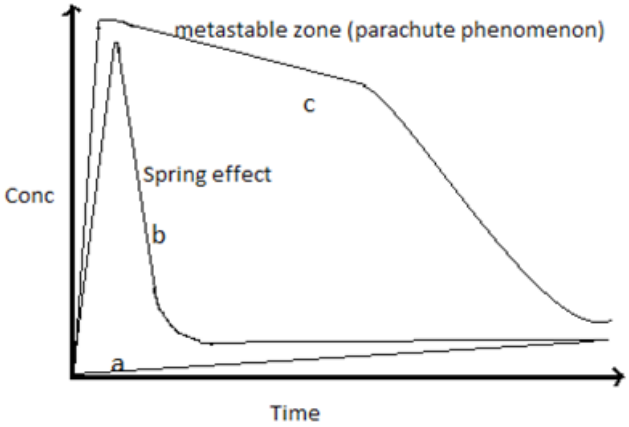

Figure 3: Spring and parachute effect to attain high solubility for insoluble drug. a) Low soluble crystalline form. b) Amorphous phase (spring form) which is short lived meta stable state shows high solubility but drops quickly to crystalline form. c) Spring with parachute effect maintained metastable state for long time results in high soluble drug form.

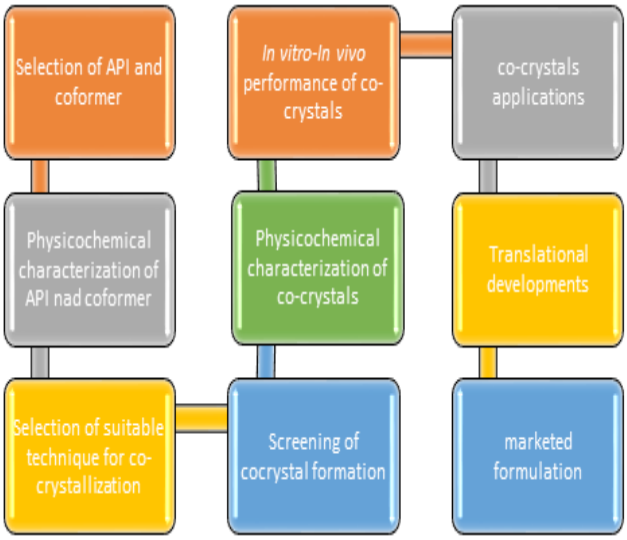

Figure 4: Design strategy involved in co-crystal formulation.

done by empirical understanding of hydrogen-bonds pattern.[76,77] The rules are (a) Crystal structure of a compound utilizes all the acidic hydrogens in the molecule for hydrogen bonding. (b) The availability of hydrogen bond donors leads to the utilization of good acceptors on hydrogen bonding. (c) Preferential formation of hydrogen bonds takes place between good donors and acceptors. N-H…O, N-H…Cl, N-H…H are some of the groups which can lead to the formation of hydrogen bonds. During designing of co-crystals, many worthful reference resources are containing empirical as well as theoretical resources such as CDS, HSP, Hydrogen bond theories and other empirical conclusions.

Cambridge structural database

Proper knowledge of intermolecular interactions is required for the synthesis of supramolecular synthons. Designing of synthons can be done by utilizing the information about hydrogen bond patterns of crystal lattice[78] which can be done by CSD. Intermolecular interactions on crystals can be studied by using which provides the information for systematic analysis of a wide range of related structures which could not be done by other methods.[79] CSD contains information about the functional groups that result in the formation of supramolecular synthons.[80]

Hansen solubility parameter

Prediction of co-crystal formation by using Hansen solubility parameter was reported by Mohammad M A.[81] This concept was actually proposed by Hansen C M for polymer solubility prediction in paints. HSP indicates that several individual forces compose the total energy of vaporization.[82] The co-crystal formation can be predicted by calculating the difference in total solubility parameter ($\Delta\delta t$) for API and co-former. These $\Delta\delta t$ values more than $10MP^{0.5}$ indicates fewer chances for the co-crystal formation and less than $7MP^{0.5}$ indicates more co-crystal formation.[80]

Co-crystallization techniques

Co-crystallization technique, capable to amalgamate two or more molecules (API and conformer through non-covalent interaction and multiple API co-crystals through drug-drug interactions). Co-crystallization technique selection is the most important as the nature, properties and morphology of co-crystals formed were influenced by this process.[70,83] Co-crystallization methods based on the use of solvents, classified as solvent-based and solvent-free techniques. Among these, solvent free techniques are gaining more importance due to the possibility of a green chemistry principle association.[84] Several aspects like API and co-former, solubility, stability, liability, polymorphs, solvents, etc were taken into consideration while selecting co-crystallization method. Method scalability should also be considered for applications in the industry.[85]

Depending on the driving force, the co-crystallization method can be classified as thermodynamic and kinetic methods. Thermodynamic methods occur mainly in equilibrium conditions and take a large amount of time to finish. Some of them are co-crystallization from melting and slow solvent evaporation. For kinetic methods, occur in non-equilibrium conditions based on reaction duration and system energy. This gives rise to metastable form, having higher gives free energy. Grinding, slurry sonication, supercritical fluid technology, spray drying is some of the techniques classified under kinetic methods. Co-crystallization methods based on the use of solvents classified as solvent-based and solvent-free techniques.

Solvent based co-crystallization methods

Solvent-based methods are most commonly used due to the ability to monitoring the process and controlling the properties of the final product. Solvent selection places the most crucial step in these methods. As the solvent selected shows its impact on crystal size, shape, purity, polymorphic form and other co-crystal characteristics.[86,87] Some of the literatures reported the importance of solvent selection in solvent-based co-crystallization method.[88,89] Solvent evaporation, cooling co-crystallization, reaction crystallization, anti-solvent addition, ultrasound-assisted co-crystallization are some of the examples comes under this method.

Solvent free co-crystallization methods

Solvent free co-crystallization methods are acquiring an interest in the industry and academia, due to the feasibility of being kindred with green chemistry principles.[79] These principles endorse efficient co-crystal production with less toxic bi-products. Mechano-chemical methods, neat grinding, liquid assistant grinding, polymer assistant grinding, hot-melt extrusion, spray congealing co-crystallization are some of the methods classified under solvent-free co-crystallization. Some of the co-crystallization techniques reported were summarized in Table 2.[90-115] Some of the latest international patents were summarized in Table 3.[116-119]

There is huge number of co-crystallization techniques, among which solvent-based methods are the most commonly used due to apparatus simplicity and procedures. But they have many unfavourable circumstances due to the use of hazardous solvents and dissimilar solubilities

Table 2: Summary of reported co-crystallization techniques.			
Co-crystallization technique	**Drug**	**Co-former**	**References**
Solvent evaporation	Adefovir dipivoxil	Suberic acid and succinic acid	90
	Ezetimibe	Benzoic acid and salicylic acid	91
	Ketoconazole	Nicotinamide and 4-amino benzoic acid	92
	Carbamazepine	nicotinamide	93
	Mirtazapine	Oxalic acid	94
	Fluoxetine hydrochloride	Benzoic acid salicylic acid fumaric acid	59
	Ibuprofen	4,4-Dipyridyl Nicotinamide	95
	Itraconazole	Malic acid Tartaric acid Succinic acid	62
	Norfloxacin	Isonicotinamide Succinic acid Malonic acid Maleic acid	96
	Agomelatine	Urea Glycolic acid Isonicotinamide Methyl 4-hydroxybenzoate	97
Solvent exchange method	Aceclofenac	chitosan	98
Solvent assisted grinding	Hydrochlorothiazide	Aerosil	99
Sonic slurry method	Carbamazepine	Saccharin nicotinamide	100
Solvent drop grinding method	Diflunisal and diclofenac	Theophylline	101
Liquid assisted grinding	Lomoxicam	Catechol, resorcinol, benzoic acid, hydroxyquinone and 2,4 dihydroxy benzoic acid	102
Dry grinding	Paracetamol	Trimethylglycine	103
Solution crystallization	Febuxostat	Urea, nicotinamide, acetamide, p-amino benzoic acid, saccharine	104
Slurry method	Quercetin	Caffeine, isonicotinamide, theobromine	105
Solvent change method	Irbesartan	Chitosan	106
Liquid assisted grinding	Curcumin	Resorcinol and pyrogallol	107
Solvent assisted grinding	Indomethacin	Saccharin	49
Neat grinding, slow evaporation and wet granulation	Niclosamide	Caffeine, urea, theophylline, para amino benzoic acid, nicotinamide, isonicotinamide	108
Solution, slurry and solvent drop grinding method	Meloxicam	Aspirin	109
Spray drying technique	Efavirenz	Glutaric acid	110
Supercritical fluid enhanced atomization technique	Theophylline, Indomethacin, Caffeine, Sulfamethazine, Aspirin, Carbamazepine	Succinic acid	111
Sublimation method	Urea	Succinic acid	112
Electrospray technology	Carbamazepine	Nicotinamide	113
	Itraconazole	Fumaric acid, Succinic acid	
Solvent evaporation	Glibenclamide	Tromethamine	114
Hot melt extrusion	Carbamazepine	Soluplus®	115

Table 3: Latest international patents on cocrystals.				
Date	**Compounds**	**Assignee**	**Patent no.**	**Reference**
9 Nov, 2017	dl – Proline and Dapagliflozin	Aurobindo pharma limited	W02017191539A1	116
31Aug, 2017	Lorcaserin hydrochloride and organic diacid	Enantia, S. L	W02017172811A1	117
6 Jul, 2017	Adipic acid and agomelate	Leiutis pharmaceuticals Pvt, Ltd	W02017144598A1	118
6 Oct, 2016	Ibrutinib and carboxylic acid	Ratiopharm Gmbh	W02016156127A1	119

of co-crystal components. Careful selection of methods is important for a specific system.

Characterization and quality control

Recent researches aimed at improving the storage stability, processing and dissolution of the pure drug during the development of pharmaceutical formulations.[120,121] New regulatory guidelines from the FDA and EMA aimed at pharmaceutical co-crystal development, which should be facilitated with the requirements and approval procedures.[122,123] Characterization and quality control of co-crystals were emphasized as important by these guidelines.

Screening of co-crystal formation

Liquid-assisted grinding has shown most attractive due to its short processing times, small sample sizes and a wide variety of applicable compounds.[124] Its application to mixtures containing drug and possible co-formers results in systematic the screening of co-crystals.[124] Thermal analysis and PXRD have been used during screening process for solids characterization.[125] Faster detection of co-crystal formation can be done by Raman spectroscopy.[126] Occurrence of new form at material interfaces can be shown by hot stage thermal microscopy.[127] *In-situ* monitoring of co-crystal formation can be predicted based on appropriate co-former's selection and structural information.[128,129]

Structural characterization

Structure and physical properties determination are a critical step in understanding the quality of co-crystals developed.[130,131] Several analytical techniques such as Raman spectroscopy, thermal analysis, solid-state NMR, X-ray diffractions, etc., are used for these estimations. Single-crystal XRD technique provides the detailed crystal structure which in turn helps as the theoretical basis for quality control of co-crystals. Powder XRD data provide the structural information of co-crystals.[132] Some co-crystals like caffeine/glutaric acid[133] and carbamazepine/melonic acid[134] results in multiple co-crystals or polymorphs based on preparation methods and formulation parameters. Some of the co-formers with multiple functional groups results in the formation of multiple hydrogen bonds, which leads to varied stacking arrangement in the crystal lattice.[135] The state of carboxylic groups was evaluated by using FT-IR vibrational spectroscopy.[136] Neutron diffraction provides the precise information of proton transfer within multi-component co-crystal.[136,137] Cross polarization magic angle spinning provides a more practical characterization which was a new data processing method associated with solid-state NMR.[138] X-ray photo electron spectroscopy and Raman spectroscopy mixed with density functional theories of solid-state were also being used for characterizations.[139] Yong Du, conducted a series of investigations on structural characterization of different co-crystals during their formation by using vibrational spectroscopy. These studies reported Raman and terahertz technique as a unique means for co-crystal conformation and reaction dynamics during formation,[140] FT-IR and FT-Raman could provide a theoretical and experimental standard to co-crystal characterization,[141] Terahertz absorption and Raman scattering spectroscopy are able to identify the co-crystal structure and also pH-dependent co-crystallization effect,[142] Terahertz time-domain spectroscopy and Raman spectroscopy could be able to identify molecular structural change of drug and also intermolecular hydrogen bonds interactions upon co-crystallization.[143] Co-crystals which were prepared by various techniques may contain a difference in their physical state, composition and production-related impurities. Due to this complexity, the quality maintenance of pharmaceutical co-crystal requires appropriate characterization methods.

Characterization of physicochemical properties

Product quality mainly depends on the physical properties of co-crystals can be known by multiple characterization methods.[43] Melting temperature, thermal transition crystallinity, hydrate or solvate formation information can be provided by Thermal Gravimetry (TG) and differential scanning calorimetry.[135,144] Most of the co-crystal contains the melting point different from their co-former and API's. Thermal scans using

PXRD or DSC-PXRD can identify physical changes caused during measurements. Chemical analysis of thermally altered compounds can be elucidated by HPLC, FT-IR and Raman. Solvate or hydrate characterization can be done by residual water measurement and thermal gravimetry.[43,135] Co-crystal stability can be assessed by measuring crystallinity.[145] Crystallinity of CBZ/Saccharin and Indomethacin/Saccharin co-crystals can be provided by PXRD patterns and melting enthalpy.[146]

In vitro and *in vivo performance of co-crystals*

Solubility and dissolution profiles of low soluble API's are improved by co-crystal formation.[147] The *in vivo* bioavailability of low soluble API's is also improved in animal models.[27,41] Shake - Flask method is mainly used for the evaluation of solubility of API at a given temperature in a given media.[67,148] *In vitro* characterization are conducted by the measurements of intrinsic dissolution rates.[149,150] Intrinsic dissolution rate is often a good parameter for predicting the *in vivo* performance of API.[59] Animal studies will give the information about the behaviour of the formulation. It was proved that the high concentration in the main absorption region improves the bioavailability of low soluble API's in many of co-crystal.[27,50,151] This animal study data should be evaluated carefully for the relevance to humans. Feeding conditions also influence the solubility and bioavailability of co-crystals formed.[152]

It is significant to mention that no single technique is sufficient to characterize completely the co-crystal structure and properties. Various characterization techniques integration can help to characterize or elucidate the structure and properties of co-crystalline materials. Among all the techniques vibrational spectroscopic techniques seem to be more beneficial for elucidation and characterization.

Challenges involved in translational development of co-crystals

Any drug substance, for converting into the drug product consists of pre formulation studies, prototype formulation, development of process, scale up and finally manufacturing of batches. The unique properties and structural features of co-crystals remain as challenging for developing them into drug product. These challenges can be reduced by selecting suitable co-crystal for the development. Translational development of co-crystals is a complex process, represented schematically in Figure 5.

Excipient selection

Selecting of compatible excipient is an utmost important step of the pre-formulation activity. The overall

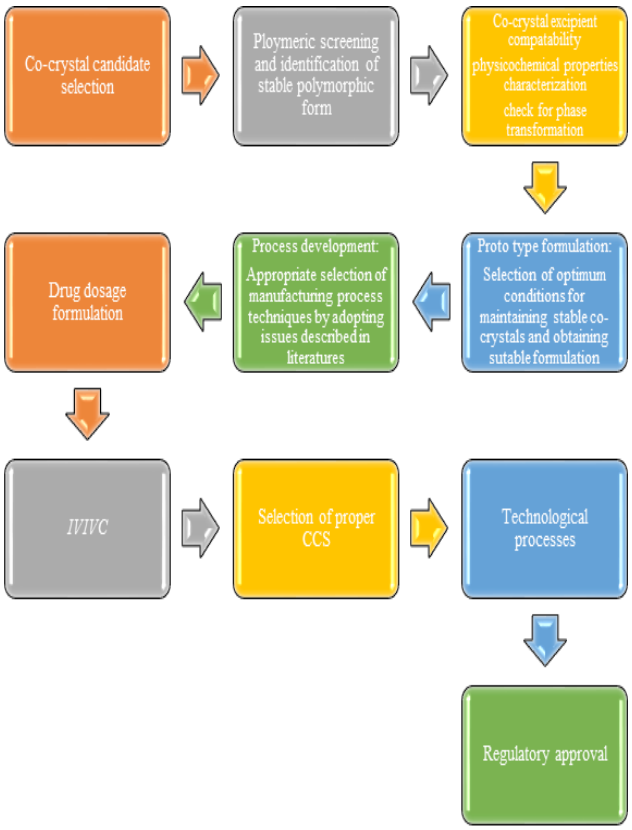

Figure 5: Schematic representation involved in translational development of co-crystals.

performance of the drug product mainly depends on the selected excipients.[153] Alhalaweh, 2014 conducted studies on celecoxib-nicotinamide co-crystals with different concentrations of SLS and polyvinyl pyrrolidone polymer, reported with the increase in bioavailability of formulation containing 1-10 % of SLS and polyvinyl pyrrolidone. The author reported the importance of use in suitable concentration of surfactant (SLS) or polymer (PVP), which in turn decreases the chance of phase transformation and increase solubility.[154] Childs, 2013 prepared DNZ-VAN co-crystal. This formation contains 1% D-α-tocopherol polyethylene glycol succinate as solubilizer and 2% Kluce LF pharma hydroxy propyl cellulose as crystallization inhibitor. This formulation showed 10-fold increase of AUC (Area under curve) when compared to parent DNZ. Whereas non-formulated DNZ co-crystals showed a modest increase of 1.7 times higher AUC in comparison with parent molecule.[75] Some literatures reported the role of additives on co-crystal performance.[155-158] Maintenance of parachute condition (prevention of supersaturation triggered precipitation) of a drug is an important aspect for co-crystal-based products. This can be achieved by selecting a polymer based on their precipitation inhibitor capacity of co-crystal and drug.[75,155-156] Selection

of suitable surfactant with optimal concentration will prevent the solution mediated transformation[64,159] and maximum apparent solubility.[75]

Prototype formulation

The aim of formulation development is to investigate the impact of excipients on the performance, manufacturability and safety of the product. Co-crystal eutectic constant K_{eu} and identification of different parameter at transition point, plays a major role in the selection and optimization of suitable excipients.[64,154,160,161] Selection of optimal pH is a crucial parameter to gain maximum solubility.[162] Normally a formulation contains diverse excipients and the effect of these excipients on product performance should be investigated by using sound statistical experiments. Constituting *in vitro - in vivo* correlation is the major challenging aspect in co-crystal product development. *In vitro* performance of the product may be hardly correlated with *in vivo* performance due to changes in the micro environment p^H, presence of endogenous surfactants, Lipids etc. which may alter the solubility of the product. Cheney, 2009 conducted, *in vitro* and *in vivo* studies of lamotrigine co-crystals with NCT. This formulation showed an enhanced dissolution rate, whereas decreased oral bio availability in rats when compared to parent molecules.[163] Establishing an appropriate formulation strategy will help in obtaining desired mechanical properties and also minimizes phase transformation of co-crystals during mechanical stress. Previous literatures stated that some of the co-crystals may undergo polymorphic phase transformation due to mechanical stress.[164] Cushioning agents like carrageenan's, alginates, chitosan's, polyethylene oxides and microcrystalline cellulose pellets may avoid the compaction induced phase transformation by absorbing the mechanical shock in tablet formulation.[165,166]

Process development

Process development is aimed at identifying the critical process parameters for ensuring the quality of the product. The selection of equipment, in-process controls and manufacturing process depends on the material properties of co-crystals. Dissociation of Theophylline co-crystals with acidic co-formers like malonic, glutaric or maleic acids will take place in the presence of water.[53] Likewise, wet granulation and wet milling operations may result in dissociation of co-crystals.[167] So, the selection of alternative operations like dry granulation and dry milling may be beneficial in these situations. Anhydrous THP-Citric acid co-crystals were converted to co-crystal hydrates within 3 days when maintained in humidity conditions.[168] This problem can be rectified by maintaining low humidity during manufacturing. Sodium naproxen -lactose-tetrahydrate co-crystals when heated from 60°C to 120°C, results in loss of water molecules from crystal lattice and transformed to co-amorphous form.[169] Therefore, adoption of the issues described in the literature should be done while selecting the manufacturing process.[170] Zhou, 2016 reported the improved solubility and tabletability of Resveratrol co-crystals, these cocrystals also shown the non-hygroscopic and phase stable even in high humid conditions, which makes them suitable for tablet formulation.[171]

Container closure systems (CCS)

The choice of selecting proper packing should be based on the nature of co-crystals and resistance against stressors. Optimized CCS can help in protecting the product against moisture, light and oxygen. AMG517: 2-hydroxy caproic acid co-crystals showed slight hygroscopic nature at 8% RH/25°C, during moisture absorption studies.[21] This problem can be rectified by adopting, humidity control, water-free process of manufacturing area and by protective packing. The selection of proper CCS may overcome some of the challenges regarding the transitional development of co-crystals. More studies should be required in this aspect.

Even though rational formulation, environment control, proper process development and selection of ccs may overcome the translational challenges of co-crystals, it is recommended to choose the most suitable co-crystal candidate for pre-formulation screening

Applications

The strategy of converting the idea of co-crystals into the application was already described in the translational development challenges of this paper.

Apixaban (AXP, trade name Eliquis®). Which could be used in various thromboembolic treatment after knee or hip replacement surgery,[172,173] having poor solubility and low oral bioavailability. There is no improvement in oral bioavailability even increasing the dose more than 25mg, which is the goal for improving the solubility.[174,175] Chen and co-workers prepared APX: oxalic acid co-crystals. Which results in better solubility when compared with anhydrous APX form. The pharmacokinetic studies of APX-OXC co-crystals shoed 2.7 times larger AUC_{0-}24h.[175]

Adefovir dipivoxil (AD, trade name Hepsera®) used against the hepatitis B virus. The drug is thermally unstable[176] and the degradation was accelerated by many factors.[176-178] The marketed formulation remains stable at room temperature[179] and converted to dehydrate form at 75% RH conditions.[180] Jung S prepared AD co-crystals with suberic acid and succinic acid as

co-formers, the thermal stability and aqueous solubility were improved in both the cases.[181] AD: Saccharine co-crystals maintained their stability throughout the storage conditions (1 month) at 60°C.[182] These studies help in the implication of the co-crystallization approach to unstable drugs and can result in longer expiry dated preparations.

P-Hydroxyacetanilide (paracetamol PA) is the most popular API used as analgesic[183,184] which exhibits poor compatibility and belongs to BCS Class-III.[185] PA co-crystals formed with different co-formers PA- Pherazine,[186] PA-trimethyl glycine,[187] PA-citric acid[188] and others[189] results in improved physiochemical, mechanical and pharmaceutical properties.

Ethenzamide (2-etoxy benzamide, ET) is a commonly used non-steroidal anti-inflammatory drug belongs to BCS Class-II, whose water solubility is low and some of the modifications may improve the property.[190-192] Many of the literatures proved that the co-crystals of ET with different co-formers showed improvement in solubility and other physicochemical properties.[193,194]

Hexamethylene bis-acetamide A is an anticancer drug used in lung cancer treatment.[195,196] Aakeroy prepared the co-crystals of Hexamethylene bis-acetamide A with a dicarboxylic acid. These co-crystals have the melting point in a range of 148°C-188°C whereas API melting point ranges between 181°C-182°C. Solubility studies showed improvement by a factor of 2.5 when compared to API.[197]

Isoniazid (INH) which is the first-generation anti-tubercular drug[198] has been reported with high solubility, whereas chemical stability in tablets is very low.[199] Many of the co-crystals such as INH: Fumaric acid,[200] INH: caffeine acid,[201] INH: Sebacic acid[202] and many other co-formers are used for INH co-crystals such as Nicotinamide, succinic acid, vanilic acid, ferulic acid, etc preparation of co-crystals act as potential drug modification for solid drug formulation.[200]

Formation of drug-drug pharmaceutical co-crystals results to overcome the problems related with a traditional combination of drugs by modifying the properties of both drugs.[59,198,203] Telmisartan: Atenolol

Table 4: Summary of pharmaceutical cocrystal products with current status.

Pharmaceutical co-crystal	components	Indication	Status or Source
Beta-Chlor®	Chloral hydrate…betaine	Sedation	Approved by FDA on 1963
Depakote®	Valproic acid… [valproate sodium]	Epilepsy	Approved by FDA on 1983
Cafcit®	Caffeine… [citric acid]	Infantile apnoea	Approved by FDA on 1999
Lexapro®	[Escitalopram oxalate] …Oxalic acid	Depression	Approved by FDA on 2002
Suglat®	Ipragliflozin… L-proline	Diabetes	Approved by FDA on 2014
Entresto®	[Valsartan sodium] … [sacubitril sodium]	Heart failure	Approved by FDA on 2015
Odomzo®	[Sonidegib monophosphate]… phosphoric acid	Basal cell carcinoma	Approved by FDA on 2015
Steglatro®	Ertugliflozin… L-pyroglutamic acid	Diabetes	Approved by FDA on 2017
Dichloralphenazone	Antipyrine… Chloral hydrate	Migrain	PubChem CID 10188
Iron sorbitex	Iron… Sorbital… Sodium citrate	Iron deficiency anaemia	PubChem CID 20715017
Nicotinamide-ascorbic acid	Nicotinamide… ascorbic acid	Vitamin complex	PubChem CID 54710212
Tetracycline phosphate	Tetracycline… phosphoric acid	Antibiotic	PubChem CID 54713149
Caffeine-sodium benzoate	Caffeine… sodium benzoate	Headache	British Pharmaceutical Codex 1907
Caffeine-sodium salicylate	Caffeine… sodium salicylate	Headache	British Pharmaceutical Codex 1907
Acridine-sulfonamide	Acridine… sulfonamide	Antiseptic	PubChem CID 54710212
TAK-020	TAK-020… gentisic acid	Bruton tyrosine kinase inhibitor	Under Phase-I Clinical trial Identifier- NCT02723201
E-58425	Tramadol hydrochloride… celecoxib	NSAID	Under Phase-III Clinical trial Identifier- NCT03108482
CC-31244	Non-nucleoside polymerase inhibitor	Non-nucleoside polymerase inhibitor	Under Phase-IIa Clinical trial Identifier- NCT0276075
T121E01F/T121E02F	Zoledronic acid co-crystals	Anticancer	Under Phase I Clinical trial Identifier- NCT01721993

co-crystals[204] proved that multidrug co-crystals could be a great replacement for standard therapy with more than one API. Almansa prepared tramadol hydrochloride: celecoxib co-crystals which showed favourable physicochemical and dissolution profiles.[205] These co-crystals completed their phase-I and phase-II clinical studies whereas phase-III is going on.[206]

Commercial co-crystal formulations

Beta-Chlor® (chloral betaine), US patent described its formulation in 1962, as its aim was to mask the unpleasant taste of chloral[207] but its co-crystal structure was revealed in 2016.[193] Zaworot Ko described chloral betain as charge assisted diol–carboxylate heterodimer. These co-crystals showed increased thermal stability when compared to pure drug.[208]

Depakene® (Valproate semi sodium) Valproate showed full potential in the treatment and prevention of scissors.[209] This is presently sold in 3 forms. Valproate: Valproic acid (free acid, trade name Depakote®), sodium valproate (salt, trade name Epilim®) and semisodium Valproate (co-crystal, trade name Depakene®).[210] Of all the several forms of valproate, the co-crystal formulation showed the superior physicochemical properties, mainly by decreasing the hygroscopicity which was found in other forms.[211]

Cafcit® (Caffeine citrate) According to British pharmaceutical codex 1907, caffeine citrate exhibits high stability in concentrated solution than pure alkaloid (pharmaceutical codex 1907). Karki, in his studies, revealed the co-crystal structure of caffeine citrate in 2007, which was previously known as complex.[168]

Lexapro® (Escitalopram oxalate) It is marketed as co-crystal which contains escitalopram oxalate salt and oxalic acid, where citalopram as hydrobromide salt, which leads to controversies regarding structural enantiomers.[212] Harrison demonstrated the patentable co-crystal from this formulation[213] recently, the Lanset reported, Escitalopram, vortioxetine is agomelatine are the most effectual antidepressants available.[214] Some of the pharmaceutical co-crystal products were summarised in Table 4

Successful drug delivery may be possible with co-crystallization. The life time of API could be enhanced through co-crystallization, further drug-drug co-crystals may be helpful to increase therapeutic efficacy by combinational therapy. Inturn, co-crystallization also enhances the chance of tablatability, stability and physicochemical properties as discussed under previous sections.

CONCLUSION

The requirement in drug properties modification is the main reason for gaining extensive attention on co-crystals. The improvement in dissolution rate, bioavailability, solubility and other physicochemical properties has been reported frequently. Research should centre in actual industry problems, such as the scaleup method for industrial standards and high throughput screening methods. Method selection is immensely important and particular for each system. A great effort is required in order to apply co-crystallization in the pharmaceutical industry as a customary method to improve drug properties. Preclinical and clinical studies have confirmed a proof-of-concept on the benefit of co-crystals. However, co-crystals may phase notable challenges in their translation to drug products. This includes co-former safety, polymorphism, lower than super saturation solubility, the behaviour of co-crystal in formulation and difficulty in conducting an IVIVC. An increase in scientific knowledge on crystal engineering and biopharmaceutical performance of co-crystals shall lead to the introduction of drug products containing co-crystals.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

API: Active pharmaceutical ingredient; **EMA:** European medicine agency; **FDA:** Food Drug Administration; **RH:** Relative humidity; **HPLC:** High performance liquid chromatography; **Hcl:** Hydrochloric acid; **Keu:** eutectic constant; **TPGS:** D-α-Tocopheryl polyethylene glycol 1000 succinate; **BCS:** Biopharmaceutical classification system; **CDS:** Cambridge structural database; **HSP:** Hansen solubility parameter; **PXRD:** Powder x-ray diffraction; **XRD:** X-ray powder diffraction; **NMR:** Nuclear magnetic resonance; **FT-IR:** Fourier transform infrared spectroscopy; **DSC:** Differential scanning calorimetry; **CBZ:** Carbamazepine; **SLS:** Sodium lauryl sulphate; **PVP:** Polyvinyl pyrrolidone; **DNZ:** Danazol; **VAN:** Vanillin; **AUC:** Area under curve; **NCT:** Nicotinamide; **TPH:** Theophyl-

line; **CCS:** Container closure systems; **APX:** Apixaban; **OXC:** Oxalic acid; **AD:** Adefovir dipivoxil; **INH:** Isoniazid; **IVIVC:** *In vivo* – *in vitro* correlation.

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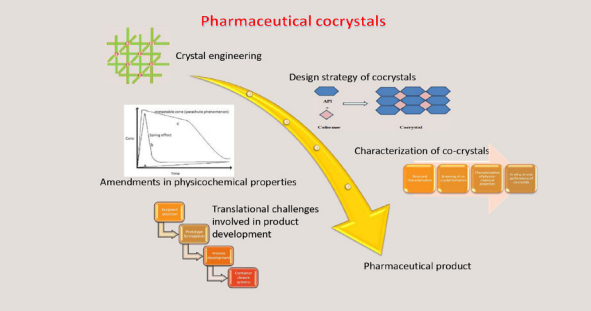
PICTORIAL ABSTRACT



About Authors

Venkata Deepthi Vemuri: Assistant Professor, Maharajah's College of Pharmacy, Phool Baugh, Vizianagaram-535002, Andhra Pradesh, INDIA.

Dr. Srinivas Lankalapalli: GITAM Institute of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, INDIA.

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