Solubility Enhancement Of Atorvastatin By Co-Crystallization Technique

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Abstract

The objective of this investigation was to study the effect of cocrystallization with different cocrystal formers on physicochemical properties of Atorvastatin calcium. Pharmaceutical co-crystal is more thermodynamically stable than crystal form of drugs.
Cocrystals were prepared by liquid assisted grinding method with Atorvastatin and different   cocrystal formers. The pure drug and the prepared cocrystals were characterized in terms of saturation solubility, infrared spectroscopy, differential scanning calorimetry. Co-crystallization alters the molecular interactions and composition of pharmaceutical materials, and is considered better alternative to optimize drug properties. In the present investigation an attempt has been made to enhances solubility of poorly soluble drug by formulating co-crystals. The Hansen solubility approach was successful for predicting the Atorvastatin calcium Co-crystals. The increase in the aqueous solubility and physicochemical property of insoluble and slightly soluble drugs is of major concern in pharmaceutical formulations. Cocrystals not only provide a technique for improvement of physiochemical property but also provide opportunity to the researchers of pharmaceutical companies regarding intellectual property. Melting point, DSC, FTIR spectra of co-crystals were different than pure drug and co-formers indicating their interaction. XRD patterns of co-crystals were not completely amorphous but less intense compared to drug alone.

Key words: *Cocrystals; liquid assisted grinding.*

Introduction

1.1 Crystal Engineering
Crystal engineering defined as 'the understanding of noncovalent intermolecular interactions between the molecules in the context of crystal packing and the utilization of such intermolecular interactions in the design of new solids with desired physical and chemical properties'.

In 1962, the basics of crystal engineering were described by von Hippel in detail under the term 'molecular engineering'. Modern crystal engineering originally commence as topochemistry for understanding the product distribution and regioselectivity in solid-state molecular reactions.

This approach has built rapidly, predominantly with the introduction of modern crystallographic techniques followed by the development of area detector technology.

Crystal engineering technique now covers many aspects of intermolecular interactions in solid state compounds, prediction of structure, control and rationalization, in addition to the novel molecular building blocks synthesis and preparation of crystalline materials, and perhaps packed up into the components of analysis and synthesis.

Crystallization process is concerned with the progress from melt of the crystalline state or supersaturation solution. Within this field primary concerns include the influence of crystallization conditions, the development of crystal nuclei. It is surrounded by the concept of the growth unit that a discrete link with the supramolecular concept of a synthon is accomplished.

This supramolecular synthons are spatial arrangements of intermolecular interactions; therefore, generally the objective of crystal engineering is to recognize and design synthons between molecules that are strong enough to be interchanged between network structures. This ensures simplification eventually leading to the predictability of one-, two- and three-dimensional patterns produced by intermolecular interactions.

The Cambridge Structural Database investigation possibly utilized to recognize stable hydrogen bonding motifs with the objective that the strongest motifs will remain intact cross a family of related structures. Amides and carboxylic acids contain functional groups which are self-complementary and capable of producing supramolecular homosynthons, however they are complementary with each other and can also interact through formation of a supramolecular heterosynthon.

This motif has been considered for in the framework of crystal engineering and the carboxylic acids interaction with heterocyclic bases is possibly the most extensively studied type of synthons.

Crystal engineering may also involve the production of spheronized particles (i.e., avoid needle-like crystals) to improve flow properties for tableting and avoid difficulties in washing, filtering and drying during primary manufacturing.

The concept of crystal engineering was introduced by Pepinsky in 1955 and implemented by Schmidt in the context of organic solid-state photochemical reactions. Desiraju subsequently defined crystal engineering as ''the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties.'' Crystal engineering has now matured into a paradigm for the preparation or supramolecular synthesis of new compounds.

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure.

 Crystal engineering affords a paradigm for rapid development of pharmaceutical cocrystals. It can be defined as an application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of self-assembly.

Crystal engineering involves modification of the crystal packing of a solid material by changing the intermolecular interactions that regulate the breaking and formation of noncovalent bonds, such as hydrogen bonding, van der waals force, π-stacking, electrostatic interactions, and halogen bonding.

Crystal engineering has now matured into a paradigm for the preparation or supramolecular synthesis of new compounds.

A crystal engineering experiment typically involves CSD surveys followed by experimental work to prepare and characterize new compounds that are sustained by molecular recognition events or supramolecular synthons.

1.2 Supra molecular chemistry and Synthon Approach to Cocrystal Design

Supramolecular chemistry is an important, interdisciplinary branch of science encompassing ideas of physical and biological processes, defined as 'chemistry beyond the molecule', i.e. the chemistry of molecular aggregates assembled via non-covalent interactions.

The term supramolecular synthon is frequently used in the research field of cocrystals. It is defined as structural units within supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions.

Supramolecular synthons are spatial arrangements of intermolecular interactions and the overall goal of crystal engineering is therefore to recognise and design synthons that are robust enough to be interchanged between network structures. This ensures generality ultimately leading to the predictability of one, two and three dimensional patterns formed by intermolecular interactions. Representative examples of pharmaceutically acceptable cocrystal formers that are able to cocrystallise with APIs include carboxylic acids, amides, carbohydrates, alcohols, and amino acids.

The term 'synthon' was initially established to explain synthetic organic structural features. In biological processes, supramolecular chemistry is nothing but non-covalent molecular binding recognized by Paul Ehlrich and Emil Fischer's lock-and-key principle through concept of complementarity and selectivity. An electropositive hydrogen bond donor move towards an electronegative acceptor, cation…anion electrostatic interaction in metal complexes and salts, and strikes in one part of the molecule fit into hollows of another portion (hydrophobic interactions).

While the fundamental recognition processes that guide aggregation of supramolecular are administrated by the same principles and forces, the chemical systems studied are generally classified into two major classes: in general molecular recognition in solution is referred to as supramolecular chemistry, and periodic arrangement of supermolecules in the solid state as crystal engineering.

In early studies, Etter and co-workers proposed several "hydrogen-bond rules," including the observations that

(1) all good proton donors and acceptors are used in hydrogen bonding, and

(2) the best donor typically pairs with the best acceptor in a given crystal structure.

The combined use of the hydrogen-bond rules with a geometric analysis (known as graph-set analysis17) assisted Etter and co-workers in implementing rational cocrystal design in the synthesis of many new supramolecular structures.

Allen et al. demonstrated a quantification of the "robustness" of a certain class of intermolecular arrangements (commonly called motifs, or synthons) involving strong hydrogen-bonded bimolecular ring motifs. Their analysis involved examining trends within the Cambridge Structural Database (CSD), a searchable repository containing more than 300,000 small-molecule crystal structures. They assessed the robustness of a motif in terms of its "formation probability," that is, the observed frequency of motif formation among all structures containing the necessary functional group components. A higher formation probability suggested a greater utility in a cocrystal design scheme. By relying on robust intermolecular interactions with demonstrated solid-state reproducibility, synthon-based cocrystal design has become increasingly important to the synthesis of new cocrystal materials.
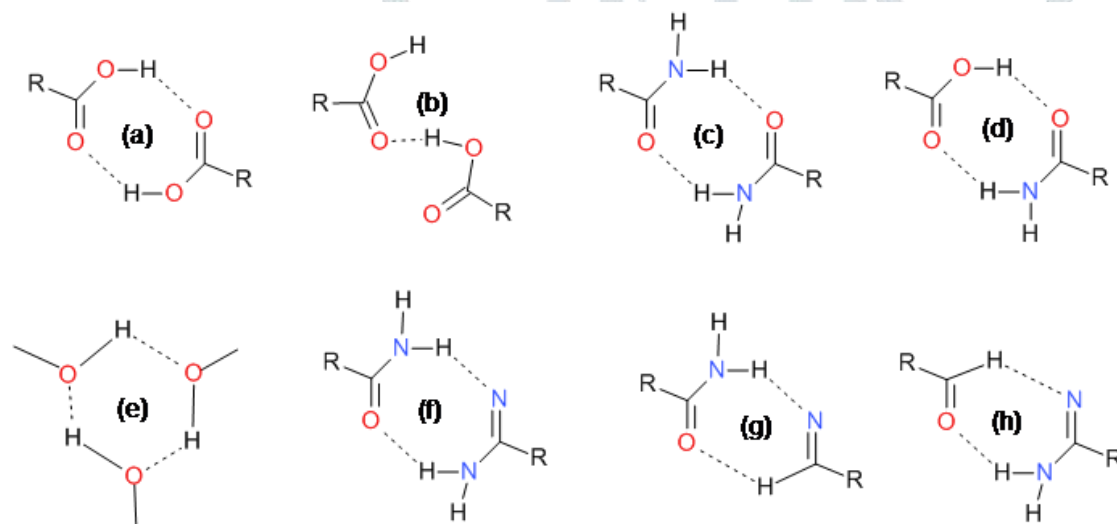
Figure 2: Showing Representative supramolecularsynthons.

(a) homosynthons exhibited by carboxylic acid,

(b) head-to-tail chains formed from carboxylic acids,

(c) homosynthons exhibited by amide dimmers,

(d) heterosynthon exhibited by acid-amide dimers,

(e) six membered intramolecular hydrogen bond ring formed in preference Hydrogen Bonding Rules,

(f) strong synthon with N–H…O and O–H…N interactions,

(g) less favoured synthon with one weak C–H…O and one strong hydrogen bond,

(h) weak synthon observed in co-crystals with diols.

1.3 Co-crystals

Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Physiochemical properties of pharmaceuticals can be improved by obtaining co-crystals using co-crystallization. Co-crystallization with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior.

Cocrystals can be defined as homogeneous solid phases containing two or more neutral compounds in a crystal lattice with defined stoichiometry, which are solids in their pure form at ambient conditions.

The combination of an API with a pharmacologically benign co-former offers an additional dimension by which the physical properties of the solid, such as stability, solubility and dissolution rate, can be tailored to a given formulation or end-use. Specifically, co-crystals have been developed to modify and increase API solubility, to improve physical stability, and to increase API plasma levels in animal tests. Co-crystals are self-assembled at the molecular scale and can significantly expand the number of crystal forms of a given API over polymorphs, solvates and salts.
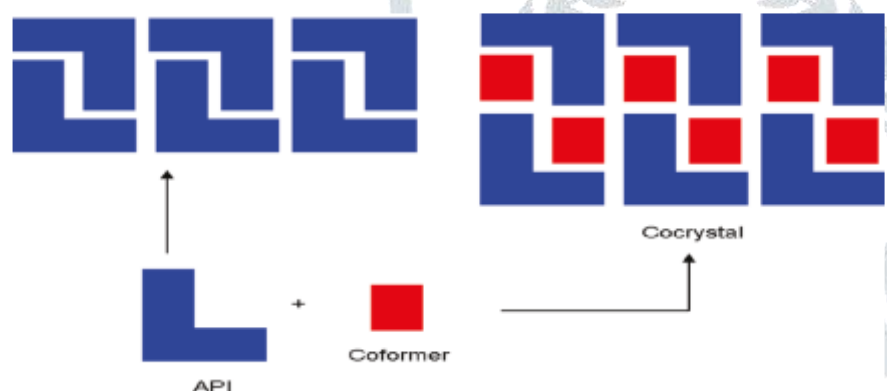
Figure 3: A cocrystal is a stoichiometric molecular complex of a molecule (blue) with a coformer (red) assembled via noncovalent interactions, predominantly hydrogen bonds.

In a pharmaceutical cocrystal, the molecule is an API and the coformer is a GRAS compound. Crystallization of the API gives the reference drug form, whereas cocrystallization leads to multicomponent crystal structures (cocrystal).

1.4 Pharmaceutical Co-crystals

A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former. Co-crystal former may be an excipient or another drug.

Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientists showed that modifying the

physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility.

Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability, hygroscopisity, and compressibility without alternating their pharmacological behavior.

Pharmaceutical co-crystals are defined as multiple component crystals in which at least one component is molecular and a solid at room temperature (the co-former) and forms a supramolecular synthon with a molecular or ionic API. Numerous APIs that exhibit undesirable solubility or stability and possess multiple hydrogen-bonding sites have been (or potentially can be) studied in the context of co-crystallization.

Pharmaceutical cocrystals, a recent addition to the class of crystalline solids, are generating increasing interest, and offer an alternative means of improving the physicochemical properties of an API.

Cocrystallization offers several key advantages:

(1) cocrystals are crystalline with definite stoichiometry, leading to better solid-state stability and more predictable physical properties and performance than amorphous solids;

(2) cocrystal design involves altering hydrogen bonding motifs rather than making or breaking covalent bonds, thus retaining the safety and pharmacological profiles of the drug molecule;

(3) cocrystals of all types of APIs (weakly acidic or basic or non-ionisable) can in principle be prepared, in contrast to salt formation technology;

(4) greater diversity is possible with cocrystal solid forms because of the availability of numerous coformers (food additives, preservatives, pharmaceutical excipients, and other APIs);

(5) cocrystals offer patenting opportunities because they are new solid forms of APIs;

(6) cocrystals can be generated using green production technologies such as grinding.

Physicochemical Properties of Cocrystals

1.1 Melting point

Melting point is amongst the physicochemical properties of co-crystals. It is the temperature of solid and liquid phase equilibrium. When the co-crystals are formed the melting point changes and comes in between the melting point of two individual molecules. If such results are obtained it can be confirmed that the co-crystals are formed. This can be explained by considering the example of two systems of cocrystals one is the optically active form and the other is the racemic form of 2-phenylbutyric acid and 2-phenylpropionic acid. These two are co-crystallized with isonicotinamide. On carrying the melting point detection it was found that the racemic group had a higher melting point than the optically active form. This result can be correlated with the denser packing arrangement inherent in centrosymmetric space groups.There are complex correlations between the melting point

of pharmaceutical product and its processability, solubility and stability. Much research work has been carried out to investigate if the melting point of a cocrystal changes with respect to the individual components and if the melting points can be estimated and modulated within a series of cocrystals. For example, the melting points of cocrystals to the API AMG517 (an insoluble small molecule VR1 (vanilloid receptor 1) antagonist) and their respective coformers showing that all these cocrystals have a melting point that fell between the melting point of the API and their correspondent conformers. In another example, it is hypothesised that the melting point and aqueous solubility of an API may be able to be finely tuned by cocrystallising this API with a series of conformers which have similar structure but show different melting points. This hypothesis was demonstrated by cocrystallisation of hexamethylenebisacetamide, an anticancer drug, and five different even-numbered aliphatic dicarboxylic acids, in which a series of cocrystals with the desired structural consistency were successfully synthesised, showing that the melting points of these five cocrystals were directly related to the melting points of the dicarboxylic acids. Although the solubility of the five cocrystals did not produce a linear correlation as the melting points did, the trend in physicochemical properties of the cocrystals can certainly be rationalised in terms of the properties of the dicarboxylic acids. From these results, it can be concluded that cocrystals may therefore offer unique opportunities for developing new solid forms of drugs in which a variety of desired physicochemical properties can be tuned in a predictable manner.

If available, differential scanning calorimetry (DSC) is the preferred technique for obtaining comprehensive melting point data, over a standard melting point apparatus or Kofler method, because additional thermal data such as the enthalpy of fusion can be determined.

For example, the melting point and heat of fusion, both determined from DSC, are necessary when attempting to characterize a polymorphic pair of compounds as monotropic or enantiotropic.

It is standard practice to determine the melting point of a compound as a means of characterization or purity identification; however, within pharmaceutical sciences, the melting point is also very valuable due to its correlations to aqueous solubility and vapor pressure. In fact, the melting point has been directly correlated to the Log of solubility, although assumptions pertaining to the entropy of fusion had to be drawn. Thus, being able to determine the melting point of a particular API before it was synthesized would be very beneficial in order to tailor its aqueous solubility toward a particular function. Unfortunately, correlations relating chemical structure directly to melting point data remain elusive. Given the number of factors contributing to the melting point of a crystalline solid including, but not limited to, the molecular arrangement within the crystal lattice, molecular symmetry, intermolecular interactions, and conformational degrees of freedom for a molecule, one clearly sees the difficulties in attempting to draw strict comparisons from molecular structure to crystalline lattice energy to melting point. The situation only becomes more complex when observing multicomponent systems because each component has its own characteristic properties and those can influence the environment (and intermolecular interactions) around its neighbors. In this section we will examine the thermal behaviour of cocrystals in which one component is an API, although findings and trends should be translatable to all cocrystalline materials.

1.2 Solubility

Co-crystallization is a technique most frequently used when the main aim is to enhance the solubility.

Solubility is another important parameter for evaluating the properties of a pharmaceutical cocrystal. Traditional methods for improving solubility of poorly water-soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). However, there are practical limitations with these techniques. Researcher tried to improve the solubilities of two APIs, exemestane (EX) and megestrolacetate (MA), in which two novel cocrystals, exemestane/maleic acid (EX/MAL) and megestrol acetate/saccharin (MA/SA), were prepared from organic solutions with different particle sizes. Co-crystallization of the EX and MA improved initial dissolution rates compared to the respective original crystals. Cocrystal EX/MAL showed a high dissolution rate even with large particles. Cocrystal MA/SA showed supersaturation with fine particles. The supersaturated concentration of MA from MA/SA cocrystal at 15 min was about six times greater than the saturated concentration of fine MA and was two times greater within 4 h. The transformation from cocrystal EX/MAL toEX was observed within 1 min in suspension. Cocrystal MA/SA was transformed to MA within 2–4 h, indicting the mechanisms of dissolution enhancement for the two drugs were different. With cocrystal EX/MAL, a fine particle formation resulted in enhancement, whereas with cocrystal MA/SA, enhancement was due to the maintenance of the cocrystal form and rapid dissolution before transformation to the original crystal. Although pharmaceutical cocrystals have emerged as a potential solution to improve the solubility of poorly soluble APIs and extensive work has been undertaken to explore new cocrystals, less research and fewer results have been published on the theoretical aspects in this area. It was found that cocrystal eutectic constants (Keu), the ratio of solution concentrations of cocrystal components at the eutectic point, were valuable to guide cocrystal selection, synthesis, and formulation without the material and time requirements of traditional methods. Moreover, Keu values can be used to predict the cocrystal solubility in pure solvent and phase behaviour as a function of solvent, ionization, and solution complexation. Understanding how cocrystal solubility-pH dependence is affected by cocrystal components is important to engineer cocrystals with customised solubility behaviour. In one study, equations that describe cocrystal solubility in terms of product solubility, cocrystal component ionization constants, and solution pH are derived for cocrystals with acidic, basic, amphoteric, and zwitterionic components.

1.3 Stability

Stability is an important parameter to be considered for any formulation. Hence in case of cocrystals it is also important to ensure the chemical stability, solution stability, thermal stability and relative humidity stability. The relative humidity stability of the cocrystals can be analysed by water absorption/desorption experiments.

The relative humidity stress test is used toidentify the best storage conditions for theproduct because the amount of water presentin the cocrystal can lead to qualitydeterioration. It was found that betterperformance of the cocrystals was displayedduring water sorption/desorption experiment.

For example, negligible amount of water was sorbed by indomethacin saccharin cocrystals in dynamic vapour sorption and desorption experiments. Cocrystals of glutaric acid and 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide sorbed less than 0.08% water up to 95% relative humidity over repeated sorption/desorption cycles. Results showed that these cocrystals are stable with respect to moisture under normal processing and storage conditions. Thermal stress and chemical stability are relatively less studied areas about cocrystal properties. Very few reports were found and these limited studies showed that thermal stress studies can provide valuable information about physicochemical stability. Meanwhile, assessing chemical stability of cocrystals is important when developing of these materials.

1.4 Intrinsic dissolution

Co-crystallization is a new technique for solubility enhancement mainly used in case of BCS class II drugs. One cocrystal example, a low solubility API, 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4-carboxamide, was cocrystallized with glutaric acid to achieve 18 times higher intrinsic dissolution rate.

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. Most of the APIs studied for co-crystallization are classified as BCS (Biopharmaceutics Classification System) class II drugs, which have high permeability and low solubility. Thus, intrinsic dissolution rate is a good indicator for in vivo performance of APIs. Although the intrinsic dissolution rate is an important parameter to be investigated, it may become more complicated with cocrystals.

1.5 Bioavailability

In pharmacology, bioavailability is a measurement of the extent to which a drug reaches the systemic circulation. The ultimate goal for cocrystal investigation is to improve the bioavailability of an API. Animal bioavailability is an important parameter to consider when preparing new forms of a compound.

Methods of Preparation of Cocrystals:

1.1 Solvent drop grinding

Modification of solid grinding technique is this technique where two materials can be grinded by adding a minor quantity of solvent. The criteria of this technique being the solvent added is in very minute quantity which when added acts as a catalyst but does not form a part of the end product. The usefulness of solvent-drop grinding was first demonstrated in the context of co-crystallization rate enhancement in a system involving several cocrystals of nitrogenous bases with a cyclohexane tricarboxylic acid derivative, all of which were initially prepared by solution growth. It was found that some cocrystals could be readily prepared by solid-state grinding, whereas

others exhibited only minor cocrystal content after grinding together starting materials for a significant time. For those that did not proceed to completion upon solid-state grinding, it was found that solvent-drop grinding could be used to prepare an essentially phase-pure cocrystal material after significantly reduced periods of time.

1.2 Solvent evaporation

Solvent evaporation is the most conventional method in case of crystallization. In this technique the material is mixed with the common solvent and evaporated completely. In evaporation stage the solution of molecules are expected to undergo various hydrogen bonding reactions. But in case of co-crystallization which consists of API and conformers solubility of both in the selected solvent plays a great role. If the solubility of the two is not similar, then the one with low solubility than the other will precipitate out. This does not mean that solubility alone is the criteria for success. Considering the polymorphism of the compound of interest is also very necessary. If the polymorphism existed then changes are that the compound after co-crystallization may convert into a form which can bridge with the co-former. But the main point to be considered is the ability of the molecule to participate in the intermolecular interaction to form a co-crystal. The intrinsic dissolution rate was increased of Fluoxetine hydrochloride by using multiple conformers like succinic acid, fumaric acid and benzoic acid. Norfloxacincocrystals were synthesized with Isonicotinamide, Malonic acid and maleic acid as conformer. The major disadvantage of this method is that it requires large amount of solvent.

1.3 Slurry conversion

Experimentations in slurry conversion were carried out in different organic solvents and water. 100 to 200 ml of Solvent was added and the resulting suspension was stirred at room temperature for few days. After few days, the solvent was decanted and the solid product was dried under a flow of nitrogen for few minutes. The remaining solids were then characterized using PXRD analysis.

1.4 Antisolvent addition

This is one of the precipitation methods for co-crystallization of the co-crystal former and drug. In this method, solvents include buffers (pH) and organic solvents. For instance preparation of aceclofenac-chitosan co-crystals, in which solution of chitosan was prepared by soaking chitosan in glacial acetic acid for few hours. By using high dispersion homogenizer the drug was dispersed in chitosan solution. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.

1.5 Twin screw extrusion

The application of twin screw extrusion (TSE) in the continuous production of cocrystals has been demonstrated for four model cocrystal-forming systems. Moreover, extrusion was found to be an effective method to make cocrystals, whether or not the mechanism of formation involved eutectic formation. TSE provides highly efficient mixing and close material packing of components which in turn lead to improved surface contact

between components, thereby, facilitating cocrystal formation without the use of solvents. Further, liquid-assisted extrusion has also been demonstrated and the addition of small amounts of benign liquids adds another processing dimension to the extrusion process, thereby, allowing for further flexibility in optimizing cocrystal production using TSE. Liquid-assisted extrusion offers advantage of promoting cocrystal formation at lower temperatures. Unlike other mechanical mixing procedures, TSE is a continuous process and lends itself to practical scalability. Thus, extrusion can be considered an efficient, scalable, and environmentally friendly process for the manufacture of cocrystals which provides a viable alternative to solution crystallization processes. 40 Carbamazepine-nicotinamide cocrystal solid dispersions preparation with polymer carriers by melting method (and/or hot melt extrusion) has been reported. During solvent free continuous cocrystallization, drug and co-former gravimetrically fed into a heated co-rotating twin screw extruder formed cocrystals. An increased conversion of the mixture into cocrystal occurred with increase in barrel temperature and screw mixing intensity. A decrease in screw rotation speed also provided improved cocrystal yield due to the material experiencing longer residence times within the process.

1.6 Sonocrystallization Method

The development of sonochemical method for preparation of organic cocrystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine-maleic acid cocrystal preparation commenced with use of ultrasound method. The comparative study of method of preparation of caffeine and theophylline as API and L-tartaric acid as coformer by Solvent drop grinding method and sonochemical method has been commenced. The results of methods were consistent hence sonocrystallization proves to be a significant approach.

1.7 Hot melt extrusion

Extrusion is useful method for synthesis of cocrystals, it involves highly efficient mixing and improved surface contacts, Cocrystals are prepared without use of solvent. The selection of this method primarily depends on thermodynamic stability of compound. This method was studied with the use of four models for cocrystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine-nicotinamide cocrystals with polymer as former. Continuous co-crystallization, API and coformer poured in the twin extruder. As a result of continuous addition of mixture the barrel temperature also increases.

Cocrystal Characterization Techniques

Cocrystal characterization is an important constituent part within cocrystal research. The basic physicochemical properties of cocrystal can usually be characterized by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

1.1 Single crystal X-ray Diffraction

SXRD is a basic characterization technique for determination of the solid state structure of cocrystals at an atomic level. However, the problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, PXRD are utilized more frequently to verify the formation of cocrystals.

1.2 Raman Spectroscopy

Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products.

1.3 Scanning Electron Microscope

SEM is a type of electron microscope that images a sample by scanning it with a high energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography.
It is applied to determine the cocrystal micrograph and particle size in many examples.

1.4 Terahertz time-domain-spectroscopy (THz-TDS)

Terahertz time-domain-spectroscopy (THz-TDS) has emerged as a versatilespectroscopic technique, and an alternative topowder X-ray diffraction in the characterizationof molecular crystals. It has beendemonstrated that terahertz spectroscopy hasthe ability to distinguish between chiral andracemic hydrogen bonded cocrystals that aresimilar in molecular and supramolecularstructure. The investigation of the cocrystal oftheophylline with chiral and racemic forms ofcoformers using PXRD and Ramanspectroscopy suggested that THz-TDS iscomparable in sensitivity to diffraction methodsand more sensitive than Raman to changes incocrystal architectures.

Prediction of Cocrystallization

1.1 The Hansen solubility parameter

Miscibility of a drug and coformer, as predicted by Hansen Solubility Parameters (HSPs), can indicate cocrystal formation and guide cocrystal screening. Predicting the miscibility of cocrystal components using solubility parameters can guide the selection of potential coformers prior to exhaustive cocrystal screening work. Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding. By definition, cocrystals are miscible systems at a molecular level. It is therefore hypothesized that an indication of the miscibility of the component molecules in the solid state could predict the likelihood of cocrystal formation.

The concept of a solubility parameter was introduced by Hildebrand and Scott, who proposed that materials with similar values would be miscible. The Hansen solubility parameter (HSP) model, which was developed later, is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding). In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets. HSPs have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces.

The solubility parameters (i.e. cohesion energy parameters) can be used to predict the physicochemical properties (such as solubility, melting point, etc.) of a material. The cohesive energy is the sum of the forces (van der Waals interactions, covalent bonds, hydrogen bonds and ionic bonds) that hold the material intact.

Cohesive energy can also be defined as the energy needed to break all these interactions, allowing atoms or molecules to detach and resulting in solid to liquid/gas or liquid to gas transformations. The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter (δ) based on regular solution theory restricted to non-polar systems, as follows:

$$\delta = (CED)^{0.5} = (\Delta Ev/Vm)^{0.5} \qquad\qquad (1)$$

where ΔEv is the energy of vaporization, and Vm is the molar volume.

δ is measured in units of $(J/cm^3)^{0.5}$, $MP_{0.5a}$ or $(cal/cm^3)^{0.5}$ where one $(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MP_{0.5a}$ or $(J/cm^3)^{0.5}$.

Attempts have been made to extend the Hildebrand and Scott approach to include polar systems and strongly interacting species such as pharmaceuticals.

One of the most widely accepted approaches, using HSPs, proposes that the total force of the various interactions can be divided into partial solubility parameters, i.e. dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h).

These partial solubility parameters represent the possibility of intermolecular interactions between similar or different molecules.

The total solubility parameter (δ_t), also called the three-dimensional solubility parameter, can be defined as follows:

$$\delta t = (\delta^2 d + \delta^2 p + \delta^2 h)^{0.5} \quad\quad\quad (2)$$

Various theoretical and experimental methods based on solubility, calorimetry, sublimation, vaporization, inverse gas chromatography and group contribution methods have been used to estimate the HSPs of a material.

The partial solubility parameters, δ_d, δ_p and δ_h can be calculated using the combined group contribution methods of Van Krevelen–Hoftyzer and Fedors as follows:

$$\delta d = \frac{\sum Fdi}{\sum Vm} \quad (3)$$

$$\delta p = \frac{(\sum Fpi)^{0.5}}{\sum Vm} \quad (4)$$

and

$$\delta h = \left(\frac{\sum Fhi}{\sum Vm}\right)^{0.5} \quad (5)$$

wherei is the structural group within the molecule, $F_{di}$is the group contribution to the dispersion forces, $F_{pi}$is the group contributionto the polar forces, $F_{hi}$is the group contribution to the hydrogen bondingenergy, and $V_i$is the group contribution to the molarvolume.

1.2 Melt (Hot stage microscopy)
Hot stage microscopy also known as MELT is an analytical technique which can be used for cocrystal characterization. Characterization of cocrystals properties is done as a function of time and temperature. As the name suggests this analytical technique is a combination of the feature of microscopy along with thermal analysis. The added features in this which offers greater possibilities of characterization of materials are image manipulation software, high-resolution color cameras and video-enhanced microscopy. The other characterization techniques along with the hot stage microscopy are used in a variety of ways to confirm transitions.
Hot-stage microscopy in the pharmaceutical industry is used in a variety of ways to confirm transitions observed using other techniques. Hot stage microscopy may be used for the evaluation of crystal forms and hydrates [14±19], solid-state characterization of bulk drugs and other physio-chemical properties. Hot melt is a visual technique hence when used with other characterization techniques such as DSC has expanded the visual collection capabilities. This visual technique is also required to confirm transitions such as melts and recrystalizations.

1.3 Scanning Calorimetry (DSC)

In this characterization technique the two specimens in which one is the sample and the other is the reference are subjected to identical temperature and an environment which is heated or cooled at a controlled rate. The energy required to obtain zero temperature difference between the two specimens is plotted and the results are interpreted. There are two types of DSC which are commonly used. The first one is the power compensation DSC where the two specimens are kept in different identical furnaces. The temperature of both is made identical by varying the power input. Thus the energy is interpreted in terms of heat capacity or the enthalpy. Other type of DSC is where both are kept in the same furnace where both the sample holders are connected by a low-resistance heat flow path. Rest of the interpretation part is same.

1.4 XRD

This analytical technique is used to provide the unit cell dimension information by phase identification. This is obtained by constructive diffraction of the monochromatic X-ray and the crystalline sample. The monochromatic ray is produced by cathode ray tube which is filtered and collimated to produce a monochromatic radiation and then directed towards the sample. In case of the sample preparation the sample is finely grounded such that a homogeneous sample is produced and the average bulk composition is analyzed. The sample is analyzed in terms of d-spacing. As the sample is posed to random orientation it gives a set of d-spacing. As each mineral has a different set of d-spacing the sample is thus analyzed. For all this to happen the most important thing is that the sample must obey Bragg's law ($n\lambda=2d \sin \theta$) which relates the wavelength of the electromagnetic radiation to the diffraction angle 2θ.

MATERIALS AND METHODS:

Materials: Atorvastatin calciumwas received from Lupin (Aurangabad, India) as a gift sample forresearch purpose. All the other chemicals and solventswere of analytical grade and procured from Research LabFine chemicals (Mumbai, India). All chemicals were usedas received without further purification. Naproxen (Fig. 1a) and sodium naproxen werepurchased from Sigma–Aldrich, and nicotinamide

Prediction of cocrystallization

Liquid Assisted Grinding (LAG)

Co-crystals were prepared using this method by first preparing physical mixture of drug and co-crystal former (CCF) with stoichiometric ratio. To this mixture, few drops of solvents (methanol) were added, mixed well using spatula and resultant mixture was then ground for 20 min in glass mortar and pestle. The milling time was kept short to avoid any degradation of the materials. At the mid-point of grinding experiment, solids were scraped from the side of the mortar wall to enable better mixing. Co-crystal prepared with molar ratio of 1:1, 1:2, 1:3, 1:4 with drug and different coformer.

Characterization of co-crystal

Analytical method development

UV spectrophotometric method development: Ultra violet absorption spectrum of Atorvastatin calcium was obtained in distilled water in the scanning range of 200-400 nm.

Preparation of standard stock solution:

The stock solution was prepared by accurately weighing 10 mg of the drug, dissolved in sufficient quantity of methanol and the volume made upto 100 ml (100ug/ml).

Preparation of serial dilutions:

- Different aliquots were taken from stock solution and diluted with distilled water separately to prepare Series of concentration.
- Absorbance was measured at 246 nm, the calibration curve was prepared by plotting absorbance versus concentration of atorvastatin calcium.

Construction of Calibration curve:

A series of dilutions from standard solution in the range of 1-5μg/ml were prepared and calibration curve was constructed at wavelength maxima of 246 nm.

FT-IR Spectroscopy:

The drug sample and Potassium bromide powder was mixed. The baseline correction of FTIR (4100 Jasco) was carried out using dried KBr and then spectrum of dried mixture of drug and KBr was recorded by placing the powder in the light path and scanning the sample over the range of 4000-400 cm^{-1}. The spectrum is shown in the figure.

Saturation solubility of API:

Saturation solubility studies were performed in triplicates according to method reported by Higuchi and Connors. For Saturation solubility, an excess quantity of drug was added to vials containing 10 ml of solvent media. The vials were then subjected to rotary shaking for 24 hours. After shaking the solution was then filtered through Whatman filter paper and the filtrate was analyzed by UV spectrophotometer at 246 nm with appropriate dilutions.

Differential Scanning Calorimetry (DSC):

Thermal analysis by differential scanning calorimetry of the drug and coformer was performed using a differential scanning calorimeter (Shimadzu). The sample powders (7-10 mg) were placed in aluminum pans,

sealed hermetically and then these hermetically sealed aluminium pans were heated at a scanning rate of 20°C/min from 50° to 350°C under constant purging dry nitrogen flow (20 mL/min). Empty aluminium pan was used as a reference.

RESULTS AND DISCUSSION

Results and Conclusion

The aim of the present research study was to explorethe possibility of employing co crystallizationtechnique in the drug and coformer and characterization of co crystal. Cocrystallization is a novel, safe and effective way toenhance physicochemical property and also solubilityof poorly aqueous soluble drugs.

Thus the concept of co crystallization isan emerging field which can serve as a milestone forsolubility enhancement and therefore deserves anurgent attention of scientific community to asses it'sefficiency and applicability.

The design of new crystal form of drugswith application of crystal engineering is an

evolving subject. Ability to design new crystalstructures will depend mostly on supramolecularchemistry and on viewing a crystal structure withinteractions of various types and strengths.Crystal engineering approach involvesidentification of interactions or supramolecularsynthons that will covers an entire family ofstructures with the object of identifying a set ofnew crystal forms of API.The development of new molecularcomplexes, co-crystal and polymorphs of drugs bycrystal engineering is becoming progressivelymore important as an alternative to saltformation, mainly for neutral or weakly ionizablecompounds. Even though lack of priority inmarketed products and concerns about the safetyand toxicity of co-crystal forming agents, there israising interest and activity in this area, whichaims to increase the understanding of crystal engineering approach.
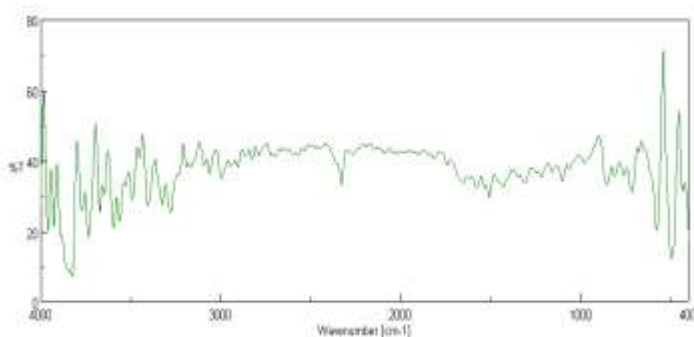
FTIR study of drug:

Figure 1: FT-IR spectra of Atorvastatin calcium

Wavenumber (cm^{-1})	Types of vibration
3648	O-H
3324	N-H
2942	C-H
1650	C=O
1311	C-N
1160	C-O
1577	C=C

Table 1: FT-IR data for Atorvastatin
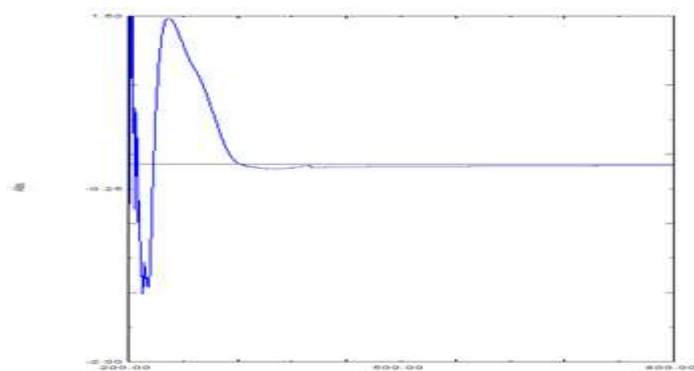
Figure7:U.V. Spectrum of Atorvastatin calcium at λmax = 246 nm.

Conc (ug/ml)	Absorbance
1	0.049
2	0.093
3	0.146
4	0.188
5	0.246

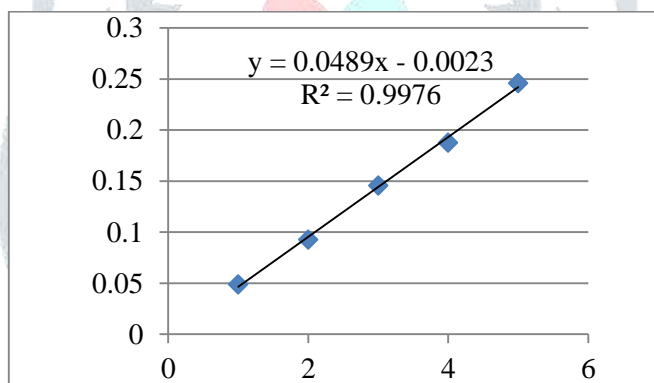
y = 0.0489x - 0.0023
R² = 0.9976

Figure 8: Calibration Curve of AT

Table 11: Absorbance data for

Calibration Curve of ATC

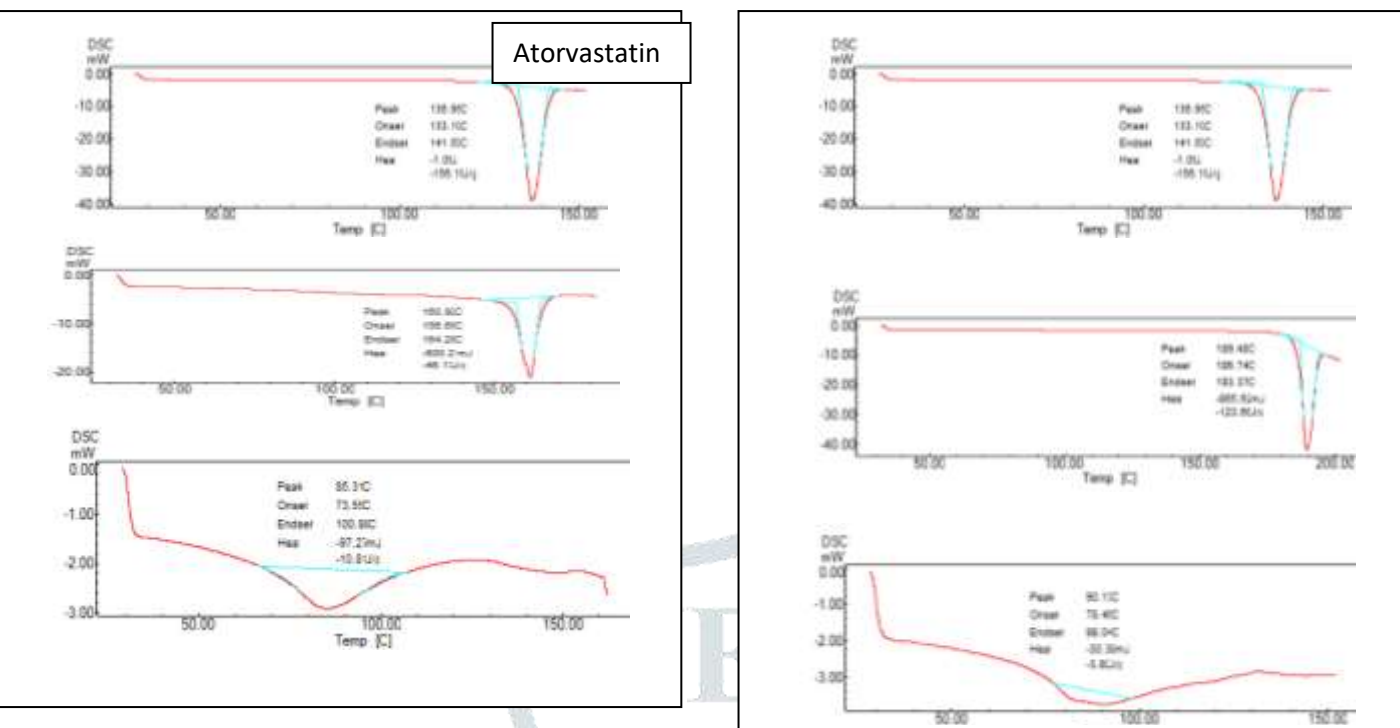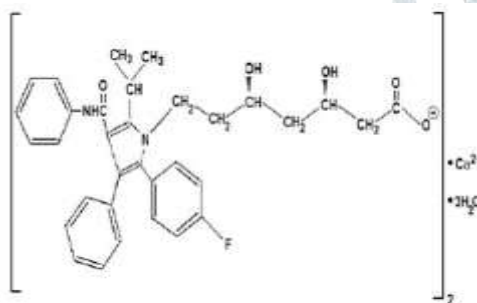## Differential Scanning Calorimetry of CCFs and Cocrystals

Table 1 : Calculation of Hansen Solubility Parameter (HSPs) of API (Atorvastatin calcium)

Atorvastatin calcium

Group	Frequency	F_{di} ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	F_{pi} ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	F_{hi} (J/mol)	V_m^a (cm^3/mol)
–CH$_3$	2	840	0	0	67
–OH	3	630	750000	40000	30
COOH	1	530	176400	50000	55.5

$-CH_2-$	4	1080	0	0	64.4
$-NH-$	1	160	44100	3100	4.5
$-N<$	1	20	640000	5000	5
$=CH$	14	2800	0	0	189
-F	1	220	-	-	22
-CO	1	290	592900	2000	10.8
-CH	3	240	0	0	-3.0
Ring closure	3	570	0	0	48
Phenylene Ring	1	1270	12100	0	52.4
Conjugation in ring	11	-	-	-	-24.2
Σ		8650	2215500	60100	494.4
Determination of Partial solubity paratmeters δd ,δv ,δh and totalsolubility parameters (δt)				δd =17.495, δp =3.0106, δh =11, δt =20.88, δv =17.75	

Prediction of Cocrystallization

Table 12: Prediction of Miscibility by Hansen Solubility Parameter

Sr. No.	COMPOUND	δd	δp	δh	δt	Δδt	REMARK
1.	Atorvastatin Calcium	17.495	3.0106	11.0	20.88	--------	----------
2.	4-hydroxy L-pyroline	20.76	9.38	21.26	31.16	10.28	-
3.	**L-Tryptophan**	**19.81**	**3.11**	**11.94**	**23.35**	**2.47**	**Miscible**
4.	D-serine	21.06	11.96	26.22	35.91	15.03	-
5.	**Nicotinamide**	**17.76**	**11.95**	**12.88**	**21.41**	**0.53**	**Miscible**
6.	Folic acid	23.12	7.66	15.64	28.82	7.94	-
7.	Aspartame	29.02	7.09	14.52	33.21	12.33	-
8.	Urea	17.28	15.65	19.55	30.42	9.54	-

9.	Threonine	17.94	7.32	20.75	28.39	7.51	-
10.	**Benzoic acid**	**19.62**	**4.35**	**10.01**	**22.45**	**1.57**	**Miscible**
11.	**Cinnamic acid**	**18.6**	**3.42**	**8.88**	**20.89**	**0.01**	**Miscible**
12.	Citric acid anhydrous	20.92	8.14	21.47	31.06	10.18	-
13.	L-Ascorbic acid	27	17.96	33.96	46.95	26.07	-
14.	L-Tartaric acid	20.25	11.4	27.22	35.79	14.91	-
15.	Oxalic acid	18.6	10.42	18.73	28.38	7.5	-
16.	**P-amino benzoic acid**	**20.78**	**4.34**	**13.56**	**25.19**	**4.31**	**Miscible**
17.	**Salicylic acid**	**20.1**	**6.22**	**15.4**	**26.07**	**5.19**	**Miscible**

Characterization of Co-crystals

Table 14: Melting point and saturation solubility of selected cocrystals:

No.	API	M.P. of CCF (°C)	Ratio	Code	M.P. of Co-crystal	Solubility (mg/ml)
1.	Atorvastatin calcium(ATC)	-	-	-	-	0.078
2.	ATC-BA	120-122	1:1	C 1	130-134	0.081
			1:2	C 2	108-110	0.121
			1:3	C 3	90-95	0.142
			1:4	C 4	80-84	0.207
3.	ATC-SA	156-158	1:1	C 5	128-130	0.082
			1:2	C 6	118-121	0.072
			1:3	C 7	87-95	0.095
			1:4	C 8	110-115	0.097
4.	ATC-CA	148 – 149	1:1	C 9	136-139	0.248
			1:2	C 10	120-124	0.291
			1:3	C 11	127-130	0.404

		1:4	C 12	135-139	0.459
5.	ATC-NIC	128-131	1:1	C 13	130-135	0.093
			1:2	C 14	140-145	0.136
			1:3	C 15	150-155	0.18
			1:4	C16	95-100	0.166
6.	ATC-PABA	187 – 189	1:1	C 17	134-136	0.182
			1:2	C 18	120-123	0.305
			1:3	C 19	124-127	0.415
			1:4	C 20	136-138	0.393
7.	ATC-L-trypto	280-285	1:1	C 21	157-160	0.09
			1:2	C 22	157-160	0.120
			1:3	C 23	152-155	0.210
			1:4	C 24	158-161	0.17

FT-IR Study of CCFs and Cocrystals
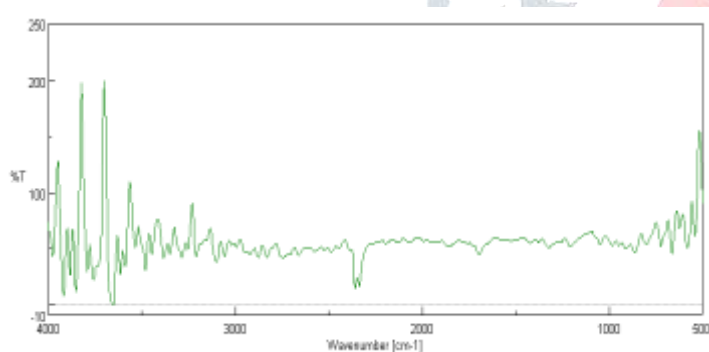
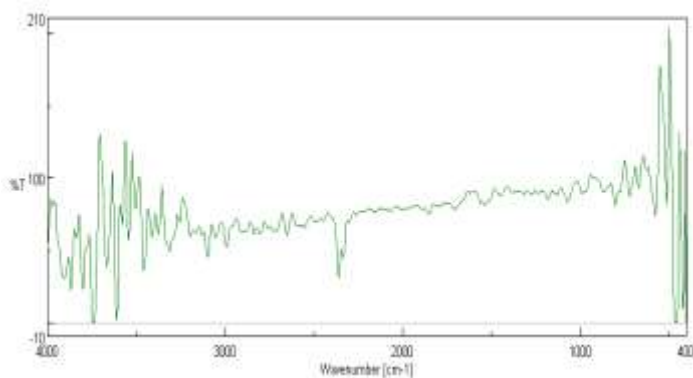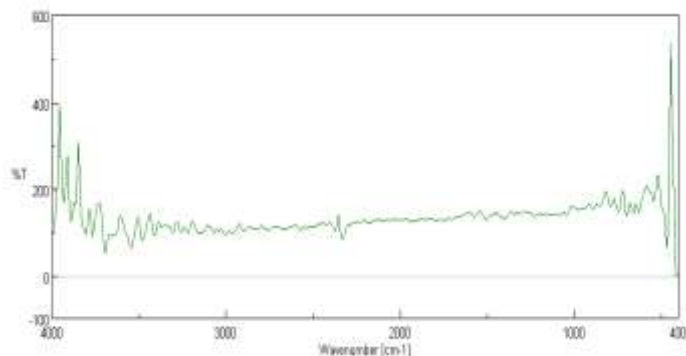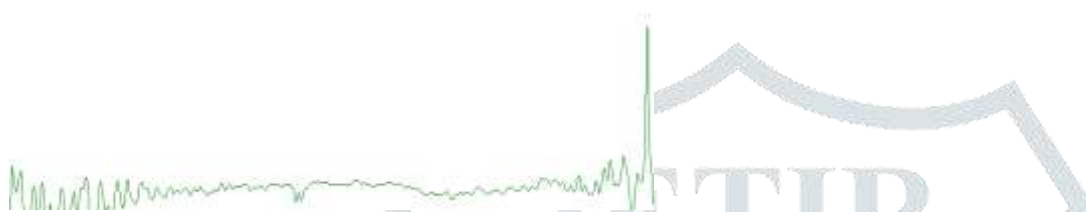**Figure 12: FT-IR spectra of Cinnamic Acid**

Figure 13: FT-IR spectra of PABA

Figure 18: FT-IR spectra of ATC: CA (1:1) cocrystal

Figure 19: FT-IR spectra of ATC: PABA (1:1) cocrystal

CONCLUSION:

In the present investigation an attempt has been made to enhances solubility of poorly soluble drug by formulating co-crystals.The Atorvastatin calcium Co-crystals prepared by liquid-assisted grinding method. The Hansen solubility approach was successful for predicting the Atorvastatin calcium Co-crystals. Co-crystals were selected on the basis of saturation solubility. Co-crystal with cinnamic acid and p-aminobenzoic acid were evaluated.

The HSP uses the miscibility tool to predict the cocrystals formation. The solubility parameters of both drug and CCFs were calculated by HSP. Depending on the solubility parameter the miscibility between the two components were predicted. The total solubility parameter indicating that materials with $\Delta\delta < 7MP_{0.5a}$ are miscible, while systems with $\Delta\delta > 7MP_{0.5a}$ are immiscible.

Saturation solubility of both ATC : PABA cocrystal and ATC : CINNAMIC ACID cocrystal increases. The miscibility between cocrystal component appears to be necessary for cocrystal formation. The aim of study was to investigate whether the miscibility predicted by HSPs can be used to predict cocrystal formation. The new cocrystals phase was confirmed by melting point, FT-IR, DSC and XRD characterization.Significant band broadening in the region of 3400-2400 cm^{-1} in FT-IR spectra and characteristic melting point alteration in DSC thermograms revealed the hydrogen bonding between drug and CCFs.

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