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## Crystal Forms of Anti-HIV Drugs: Role of Recrystallization

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### 1. Introduction

Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients (APIs) is an important aspect of drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, cocrystals and amorphous solids. Most APIs are purified and isolated by crystallization from an appropriate solvent during the final step in the synthetic process. A large number of factors can influence the crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate supersaturation and promote crystallization. For development of a pharmaceutical product, it is generally accepted that the stable form should be identified and chosen for development. However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water insoluble compounds whereas a metastable form might have advantageous properties. Moreover, the metastable polymorphs constitute local minima in the energy landscape (Figure 1) with the thermodynamically stable form being the absolute minimum at a given temperature and pressure. Thus, the search for absolute minimum and energy differences between the local minima of the drug substances is the goal of material and formulation scientists in the pharmaceutical industry. While significant efforts are made by drug development groups to identify and characterize thermodynamically stable crystal forms early in development, there are many instances where new crystal forms have been discovered later in development process. The late emergence of thermodynamically stable crystal form is often explained by Ostwald's law of stages which states that the least stable crystal form is likely to crystallize first. Metastable forms appear first during crystallization process as their crystallization kinetics is faster than those of stable forms but eventually transform into a stable form. It is important to study the transformations, because the sudden appearance or disappearance of a polymorphic form in pharmaceutical products can lead to serious consequences.

Therefore, it is of utmost importance to control the crystal formation and produce a desired form. Discovery and characterization of the diversity of solid forms of a drug substance provide options from which to select a form that exhibits the appropriate balance of the critical properties for development into the drug product. Lately, the crystal engineering approaches utilizing high throughput techniques have been applied to crystalline materials

to fruitfully generate various crystal forms of pharmaceutical compounds. The ability to engineer pharmaceutical materials with suitable solubility characteristics whilst maintaining suitable physical and chemical stability provides a driving force to utilize modern analytical tools to generate new crystal modifications.

Drugs with multicomponent crystalline phases such as cocrystals also carry desired drug properties similar to single-component polymorphs. The pharmaceutical cocrystals is defined as multicomponent molecular complex where one of the components is an investigational or marketed drug molecule (the active pharmaceutical ingredient or API) and the second component (the coformer) is a safe chemical for human consumption selected from the GRAS list of the US FDA (generally regarded as safe additive chemicals by the Food and Drugs Administration). The two components are present in a definite stoichiometric ratio and interact through noncovalent interactions, predominantly hydrogen bonds. Cocrystals have been found to offer an attractive platform to improve the solubility and dissolution rate of pharmaceuticals without compromising on the stability of the solid form. Many pharmaceutical companies are working actively on cocrystals and this is reflected by the growing number of publications and patent applications for co-crystals in recent years.

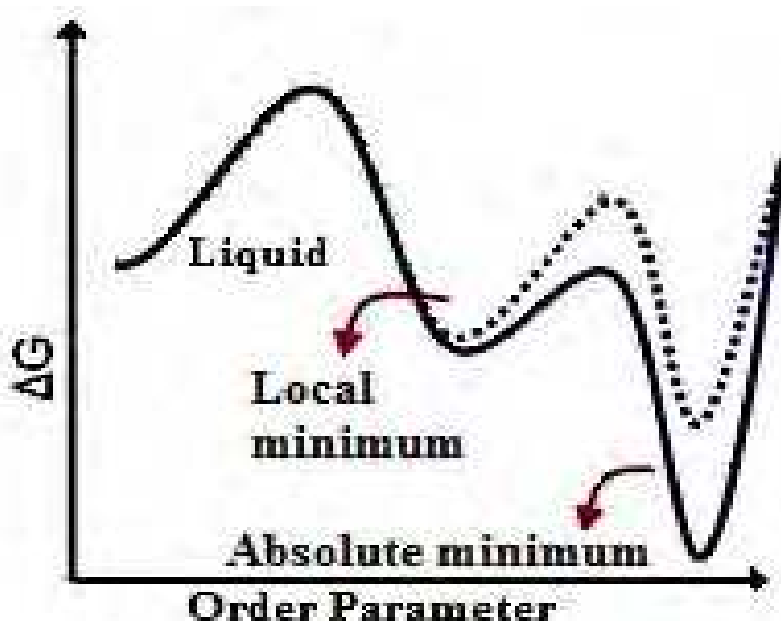
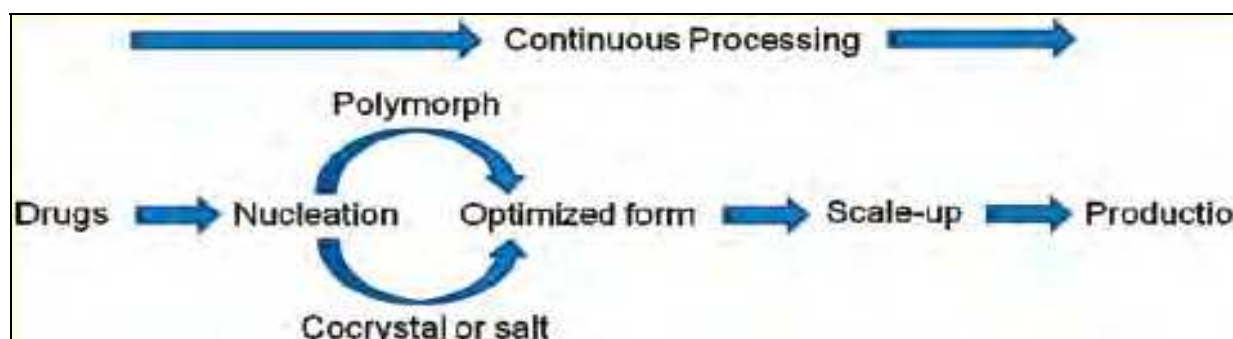


Fig. 1. Energy landscape for polymorphic forms.

The identification and characterization of diverse crystalline forms of the drug substances has become imperative for the solid state chemists in order to select the appropriate form to ensure that the product performance with respect to manufacturability, stability and bioavailability remains unchanged. Therefore, this chapter deals with the effect of crystalline state of pharmaceutical material on its physicochemical properties demonstrated through several case studies describing the phenomenon of polymorphism and a particular attention will also be paid to cocrystallization which is emerging as an important technique to generate crystal forms with improved physicochemical properties (Scheme 1).



Scheme 1. Scheme representing the path followed by drugs from nucleation to production

### 1.1 Effect of crystal forms on physicochemical properties

It is well established that different solid forms of drug molecules exist and can affect pharmaceutical drug products with respect to physicochemical properties. It is the variation in the physical and chemical properties of drug molecules that makes polymorphism such a potentially important issue for the pharmaceutical industry. The APIs with abundant hydrogen bond sites and molecular flexibility may be manipulated by proper choice of solvent to form a specific crystal form that has different arrangements or conformations of the molecule in the crystal lattice. Changing the arrangement of the molecules in the crystal lattice changes the solid state properties affecting its solubility, stability, dissolution rate and bioavailability. Different crystal forms can have different rates of uptake in the body, leading to lower or higher biological activity than desired. As a result, significant effort is placed in identifying suitable solid forms of drug substances for use in pharmaceutical drug products.

### 1.2 Crystallization process

The crystallization process of polymorphous crystals is concerned with evolution of crystalline state from solution or melts and is composed of competitive nucleation and growth. However, crystallization is a complex process which starts with the appearance of most soluble form and ends with transformation to stable form. Alternatively, the nucleation of the stable form can be initiated by the dissolution of this metastable form and growth of the stable form continues until the solubility of stable forms is reached. In many instances the metastable form with desirable properties may precipitate out which is stable for years. To selectively crystallize polymorphs, the mechanism of each elementary step in crystallization process needs to be clear in relation to operational conditions and the key controlling factors. The nucleation process is the most important for control of polymorphous crystallization. Thus control over solid form throughout the drug development process is of paramount importance.

A number of factors (Figure 2) affect polymorphic behavior of a pharmaceutical solid and type of solvent has a major factor in polymorphic selectivity and crystal morphology.

### 1.3 Effect of solvent on crystal form

Polymorph selectivity is primarily based on the polarity of the solvent. Thus a systematic approach for selecting the right solvent is beneficial for better experimental design in control

of crystallization. This effect arises from the solvent–solute interaction at the molecular level and have been explained by few of the researchers. The solvent–solute interactions during cluster formation for nucleation and growth significantly affect the ultimate crystal structure and morphology. If the solvent–solute are strongly bonded at a special crystal face, the rate-limiting step of growth would be the removal of the solvent from that face. In this case, the bonded surface grows slowly or does not grow.

However, Threlfall showed that if crystallization occurs in a region that is supersaturated with respect to one polymorph (the less soluble form) and under-saturated with respect to the other one, the solvent has no influence on the nucleation of the polymorphs and the thermodynamics will lead the process toward the production of the less soluble polymorph (Threlfall T., 2000). Moreover, the thermodynamically stable polymorph is the most stable form irrespective of the type of the solvent used. Since the thermodynamic stability of different polymorphs does not change with type of the solvent, then the solvent effect on polymorphism is attributed to the kinetic parameters.

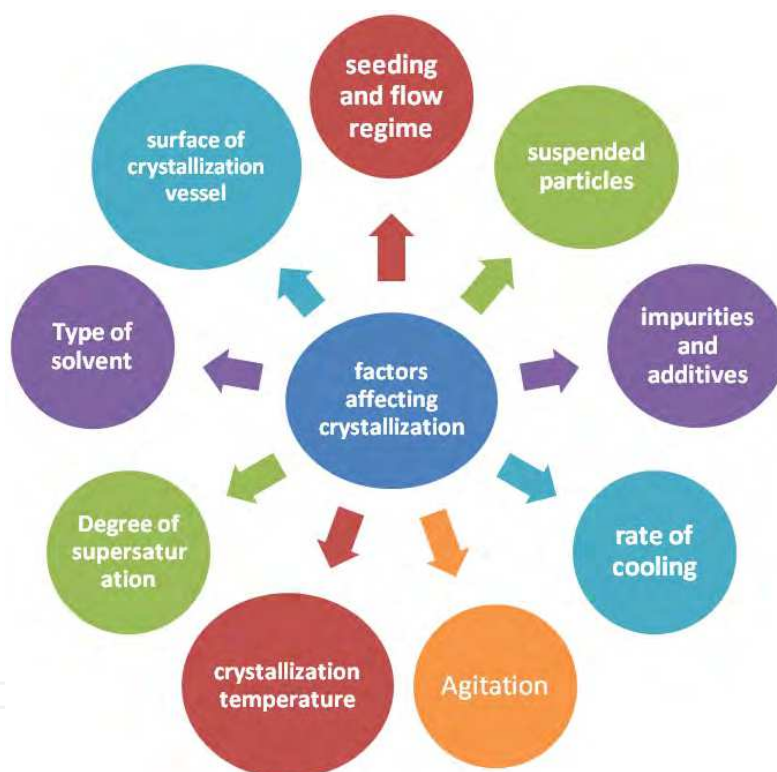


Fig. 2. Factors which affect the crystallization of a drug substance

#### 1.4 Other factors

Within the same solvent system, many factors are known to influence the crystal habit including supersaturation, cooling rate and agitation. At a constant temperature, supersaturation has a direct effect on the nucleation rate. As the supersaturation is increased, the rate of nuclei formation is greater than crystal growth and growth occurs mainly in one direction, producing elongated crystals. On the other hand, when there is lesser degree of supersaturation, solute solvent interactions are insignificant, producing platy crystals.

Similarly, rate of cooling alters the crystal habit by its influence on degree of supersaturation. Crystallization at a slower cooling rate produces more symmetric crystals compared with faster cooling. During faster cooling, nucleation is faster than crystal growth rate; therefore, many small crystals appear instead of few crystals growing to sufficiently larger size.

Agitation has also an important effect on the process of crystallization. The aspect ratio (ratio of horizontal maximum and vertical maximum distance of particle) is highest for unstirred conditions than during stirring. The crystals obtained under stirring conditions are fine since stirring facilitates the rate of nucleation by an even distribution of the solute molecules in the solvent. Increased nucleation rate is the result of collision of initial crystals with the stirrer and formation of smaller seeds for further crystallization. Additionally, stirring can also break larger crystals to smaller ones. Thus external appearance of a crystal can be altered by changing the growth environment to suit the requirements.

2. Polymorphism in anti-HIV drugs

This chapter throws light on the different crystalline forms reported so far for nevirapine, efavirenz, lamivudine, stavudine and zidovudine. Preparation and isolation methods, structural characterization and properties of polymorphic/solvatomorphic/cocrystal systems as well as phase transformations are illustrated.

2.1 Ritonavir

A number of studies have successfully demonstrated the appearance of different crystalline forms of some anti-HIV drugs upon recrystallization. An early example being that of ritonavir, marketed as Norvir. The late emergence of a thermodynamically more stable form (Form II) which unexpectedly precipitated from the semisolid capsule formulation led to the removal of the product from the market. The new crystal form (form II) appeared after conversion of metastable crystalline form I (Chemburkar et al., 2000; Bauer et al., 2001; Desikan et al., 2005; Miller et al., 2005). Ritonavir polymorphism was investigated using solid state spectroscopy and microscopy techniques including solid state NMR, near infrared spectroscopy, powder X-ray diffraction and single crystal X-ray analysis. Ritonavir was found to exhibit conformational polymorphism with two unique crystal lattices having significantly different solubility properties. An unusual conformation was found for form II that results in a strong hydrogen bonding network. Although the polymorph (form II) corresponding to the “cis” conformation has a more stable packing arrangement, however, nucleation, even in the presence of form II seeds, is energetically unfavored except in highly supersaturated solutions. The coincidence of a highly supersaturated solution and a probable heterogeneous nucleation resulted in the sudden appearance of the more stable form II polymorph.

Form	Melting point, °C	$\Delta H_{fus}$ , J/g	Solid state structure
I*	122	78.2	Monoclinic
II*	122	87.8	Orthorhombic
III	78–82	60.3	Monoclinic
IV	116	59.8	Not assigned
V	97	32.0	Monoclinic

\*Bauer *et al.*

Table 1. Comparison of physical parameters of ritonavir crystal forms



This polymorphic shift in ritonavir illustrated the need for early and comprehensive identification of solid-form diversity of this API. The polymorphic behavior of ritonavir was explored by Morissette et al (Morissette et al., 2003) in 2003 using CrystalMax, a high-throughput crystallization platform, with the aim of finding known and novel crystal forms of the drug molecule. Three additional crystalline forms of ritonavir were discovered when about 2,000 screening experiments were carried out (Table 1). These forms were found along with both known forms I and II, which were obtained from previously unreported solvent mixtures. Form III is a crystalline formamide solvate that converts to form V, a previously unknown hydrated phase, upon exposure to aqueous medium. Form V which is a trihydrate obtained from exposing the form III to aqueous conditions, in turn converts spontaneously to needle-like form I crystals. The process of preparing form I from III is an unusual route to a “disappearing polymorph” and provides a novel strategy for control of particle size and morphology. Form IV is a true, unsolvated, metastable previously unreported polymorph of ritonavir. Optical imaging (Figure 3) and *in situ* Raman spectroscopy were used to characterize newly formed crystals. Each of the novel forms found by means of high-throughput crystallization was scaled up to multiple milligram and gram levels. Thus the high-throughput crystallization for solid-form discovery and exploration of large numbers of parallel crystallization trials led to identification of more polymorphic forms of ritonavir.

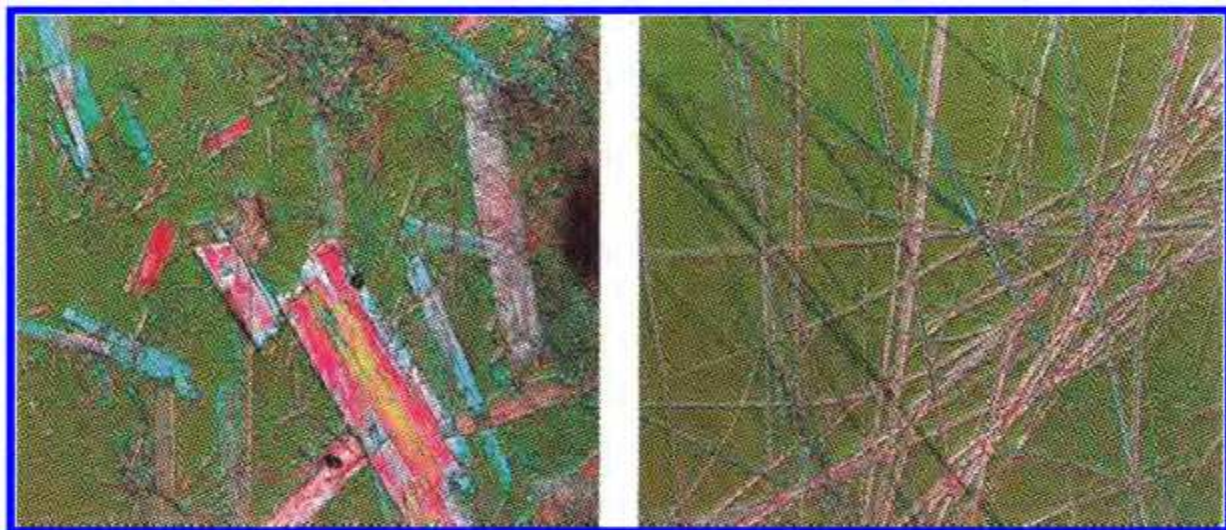


Fig. 3. Video micrograph of crystal Form I (left) and Form II (right).

## 2.2 Nevirapine

Three polymorphs and many solvatomorphs have been reported for nevirapine, a non-nucleoside reverse transcriptase inhibitor, depending upon the recrystallization method. Specifically, from a crystal engineering viewpoint, the presence of the amide function CO-NH in the nevirapine molecule indicates the possibility of alternative modes of self association, namely via a dimer or a catemer synthon, leading to crystal polymorphism, whereas interaction with the solvent molecules having complementary donor and acceptor functions result in formation of solvates, significantly extending the solid state chemistry of the drug. Form I was prepared by recrystallizing nevirapine from alcohols, ethers, esters or their mixtures while refluxing from toluene, n-butanol or methyl-isobutyl ketone and

subsequent cooling to 0-10 °C yielded form II. Form III was prepared by refluxing nevirapine in chloroform and using dichloromethane as antisolvent to the reaction mixture (Reguri and Chakka, 2005, 2006). However, many other experiments to investigate the existence of any other thermodynamically more stable form at room temperature, led to appearance of different solvatomorphs of nevirapine with varying stoichiometries depending upon the solvents selected. The first report on preparation of different solvatomorph by Pereira et al appeared in 2007 (Pereira et al., 2007). Six different solvates of nevirapine with different morphology were obtained by saturating the solvent systems with drug at room temperature and cooling in refrigerator. Despite different morphologies the DSC profiles did not show any relevant differences for raw material and other forms at crystal fusion peaks. However, a thermal event was observed below the melting temperature in NEV 3, NEV4 and NEV6 indicating the loss of some solvent molecules. The presence of solvent is confirmed by TGA and Karl fischer analysis. The authors have reported the crystal structure of two solvate forms of nevirapine, hemihydrate (NEV3) and hemiethylacetate (NEV4) (Figure 4).

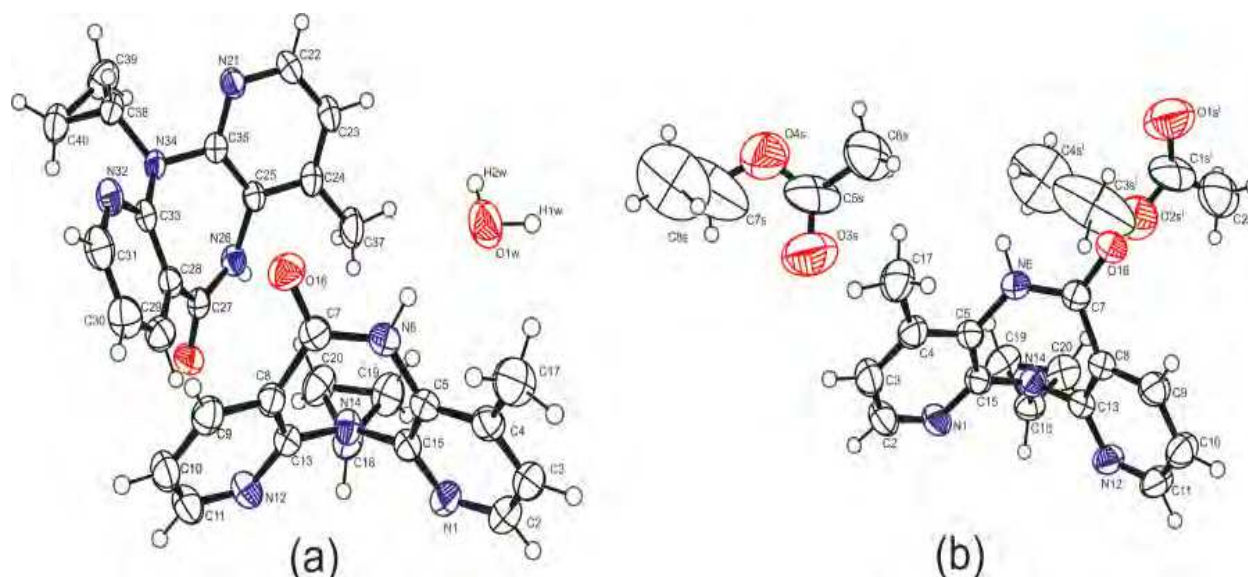


Fig. 4. Ortep representation of structure of (a) nevirapine hemihydrate and (b) nevirapine hemiethyl acetate solvate.

Caira et al have also reported five different solvates of nevirapine (Caira et al., 2008). The initial characterization of all the forms has been performed utilizing DSC and TGA. The results show that the drug molecule displays significant variability in its modes of self assembly while accommodating the different solvent molecules. The DSC results show less thermal stability for toluene solvate while ethylacetate solvate, dichloromethane solvate, hydrate and 1,4-dioxane solvate were stable. The ethylacetate solvate and dichloromethane solvate are isostructural and their dimmers are packed in identical fashion, generating continuous channels parallel to the *b*-axis that accommodate the solvent molecules (Figure 5). However, in the toluene solvate containing a larger guest molecule, the host dimers are packed in a different mode, but the guest molecules are again situated in channels.

The effect of series of alcohols on solvate formation capability of nevirapine molecule has also been illustrated by Caira et al (Caira et al., 2010). The structures of all the solvates were



based on a common isostructural framework comprising centrosymmetric hydrogen-bonded nevirapine dimers and contain a common channel parallel to the crystal b-axis in the series which accommodates the various solvent molecules. Thermogravimetric results yielded a guest-host ratio close to 0.5 for the 1-butanol solvate and a steady decrease in this ratio from 0.43 to 0.32 for other solvates. This anomalous stoichiometric variation was resolved following successful X-ray analysis of 1-butanol solvate which revealed that the length of disordered 1-butanol molecule is proportionate with the channel cavity, resulting in a stoichiometric association while in other solvates significant disorder for the solvent molecules was observed which is attributed to their increasing chain lengths being disproportionate with the channel cavity.

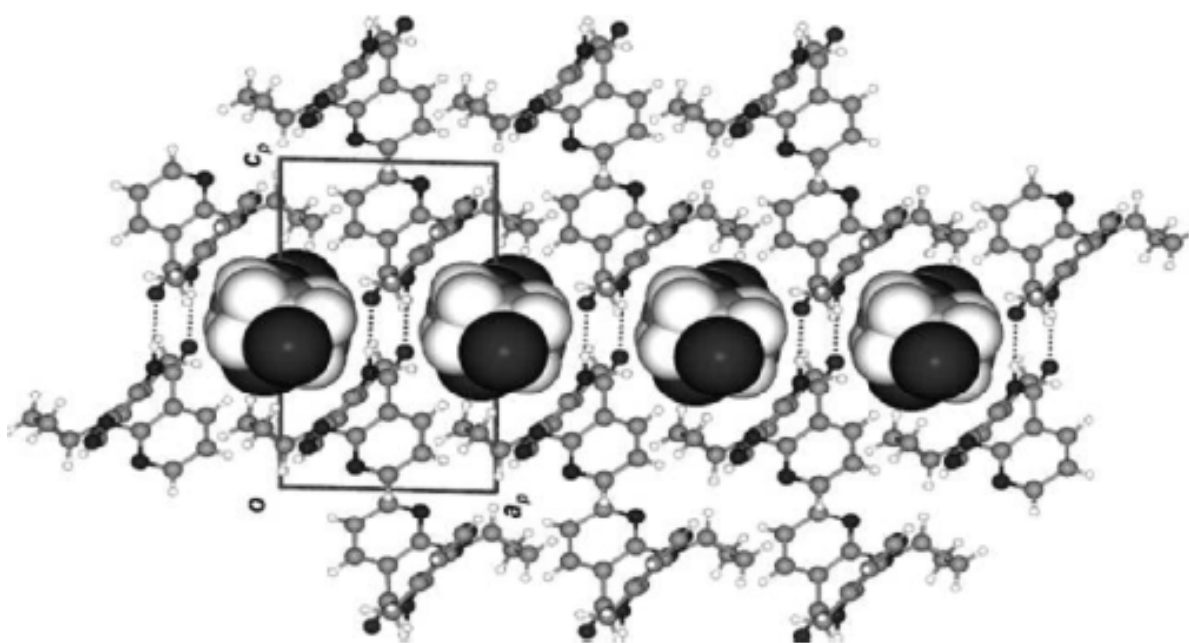


Fig. 5. Inclusion of ethyl acetate molecules within channels in crystals of solvate of nevirapine.

In the view of tendency of solvate formation of nevirapine molecule, other workers have also prepared and characterized the various solvates of nevirapine. In one of the studies, the authors have prepared the solvates by dissolving excess drug in selected solvent systems at 60 °C. However, the choice of solvent system was based on the polarity index of the solvents (Sarkar et al., 2008). Five different crystal forms have been obtained along with an amorphous form. The crystallization of nevirapine under a variety of crystallization conditions resulted in a change in the crystal habit of the drug without change in the internal crystal lattice as suggested by their similar enthalpy of fusion. The mass loss from the TGA was found to be negligible for all the solvates in comparison to the theoretical mass loss indicating that solvents used for crystallization formed weak solvates in this study. However, chadha et al have determined the binding energy of the solvent in the crystal lattice using differential scanning calorimetry which is found to be higher than the enthalpy of vapourization of the corresponding solvent for all the solvates except for toluene solvate indicating that the solvent molecules are tightly bound into the crystal lattice of nevirapine molecule (except in case of toluene solvate) (Chadha et al., 2010). These authors have also

calculated the enthalpy of solvation by determining enthalpy of solution of solvate and drug in the solvent which is entrapped in the crystal lattice of the solvate using solution calorimetry technique. The enthalpy of solution when determined in buffer system indicated that out of the six solvates formed ethanol solvate exhibited the maximum ease for molecular release of the solvent molecule from the lattice.

### 2.3 Efavirenz

The abundant hydrogen bonding sites in efavirenz, another non-nucleoside reverse transcriptase inhibitor, make it a potential candidate to exhibit crystal modifications upon recrystallization. Driven by this aspect, various authors investigated the solid-state structures of recrystallized products of efavirenz. The varying recrystallization conditions such as rate of stirring and cooling, antisolvent addition, refluxing/heating, drying under vacuum, and presence of impurities, along with solvents and/or their mixtures with varying polarity have yielded different forms of efavirenz. The patent literature till date reveals 23 different polymorphic forms of efavirenz, one monohydrate and an amorphous form although there is some ambiguity about the actual number of solid forms (polymorphs and solvates) of this API (Radesca et al., 1999, 2004; Sharma et al., 2006; Khanduri et al., 2006; Reddy et al., 2006; Dova, 2008). In these patents, inventors have claimed novel solid forms of efavirenz based on XRPD and DSC analysis. The patent data shows that Form I is the most stable form and all the polymorphs revert to this form under some condition or the other. However, the characterization of these reported forms is not adequate enough to prove them novel.

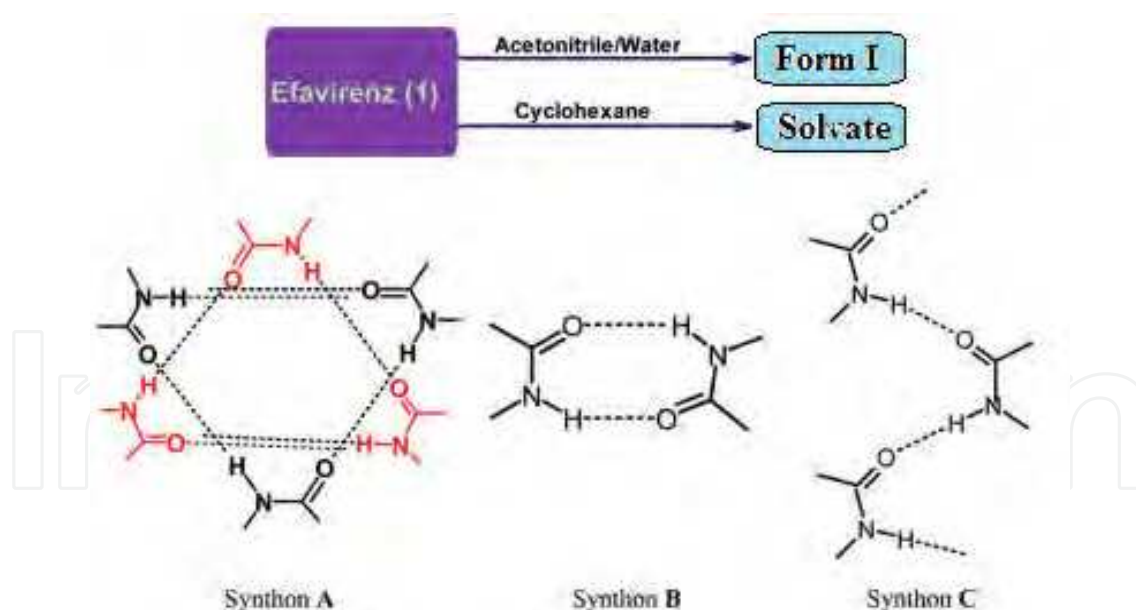


Fig. 6. Solid forms of efavirenz, their transformations and some synthons present in the polymorphs of efavirenz

Recently, two new polymorphic forms structurally characterized by single crystal X-ray diffraction have been reported by Cuffini et al and Ravikumar et al (Cuffini et al., 2009; Ravikumar et al., 2009). These two forms do not correspond to the Form I reported in various patent.

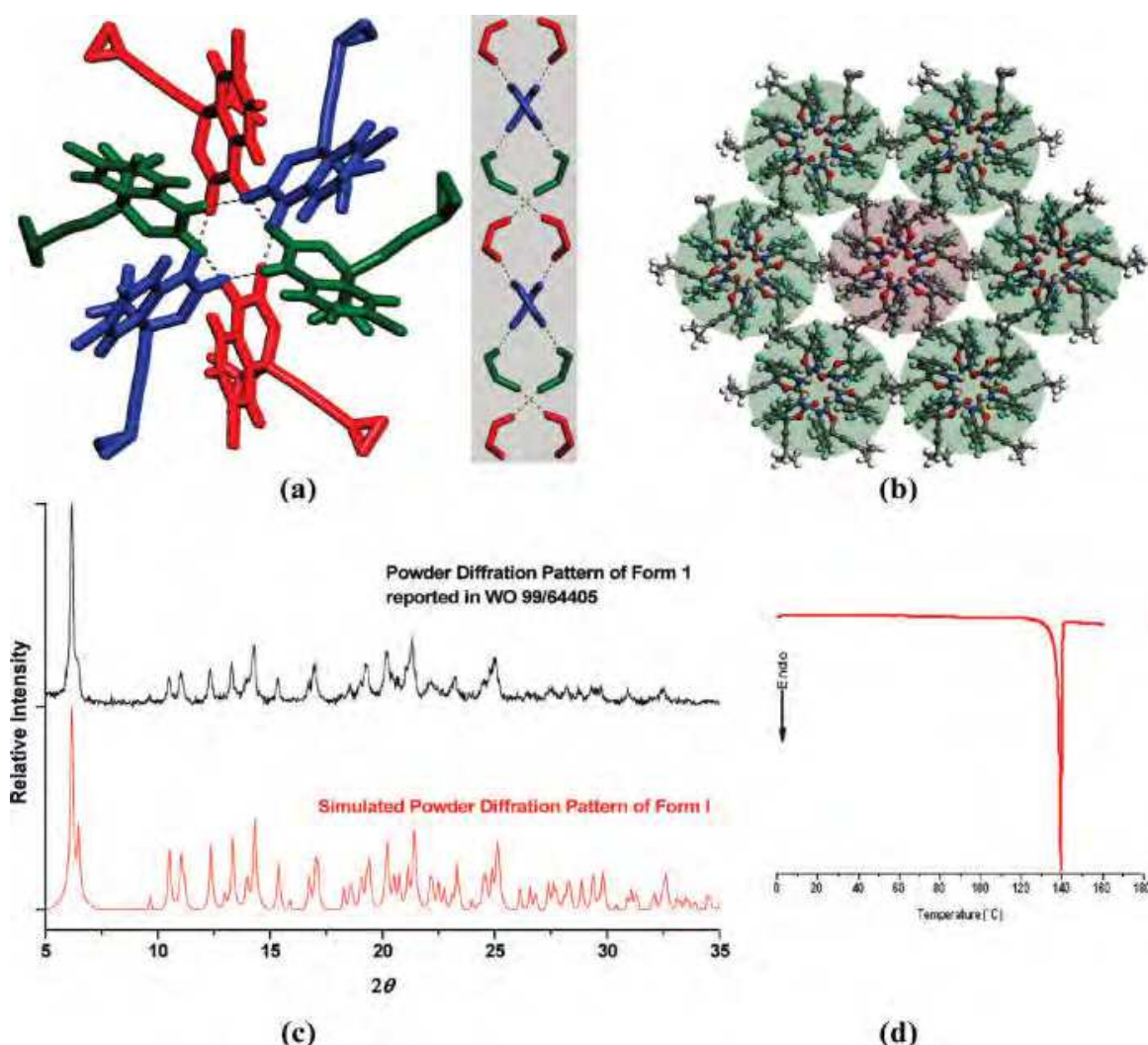


Fig. 7. Efavirenz, form I: (a) A view of the double helical chain viewed down the *c*-axis with the three symmetry independent molecules represented in red, green, and blue. The inset shows the formation of the double helical chains. (b) Hexagonal close packing of helices. (c) PXRD pattern for form 18g and form I. (d) DSC trace for form I.

The structural information of the stable Form I was first reported by Mahapatra et al (Mahapatra et al., 2010). The authors obtained this form (Form I) at the interface of an acetonitrile-water solvent system as well as from methylcyanide-water mixture (Figure 6). They also reported a solvate of efavirenz which was obtained by dissolving the drug in cyclohexane at 60 °C with stirring and leaving the solution undisturbed for 2 days after filtration to get rectangular crystals. The DSC analysis of these two forms showed that the solvate converts to Form I after desolvation. Both the forms have been further characterized using single crystal X-ray analysis. The efavirenz molecule exhibits a noticeable degree of conformational disorder in the cyclopropyl group. After exhaustive study it was found that Form I crystallized in double stranded helices stabilized by N-H $\cdots$ O molecules (Figure 7). However, in the solvate, two molecules of efavirenz form the amide dimer which are stabilized by C-H $\cdots$  $\pi$  interactions to form a bilayer stacked in three dimensions to form columns. The solvent molecules are lined in these columns and are stabilized by interactions with CF<sub>3</sub> and cyclopropyl residues (Figure 8).



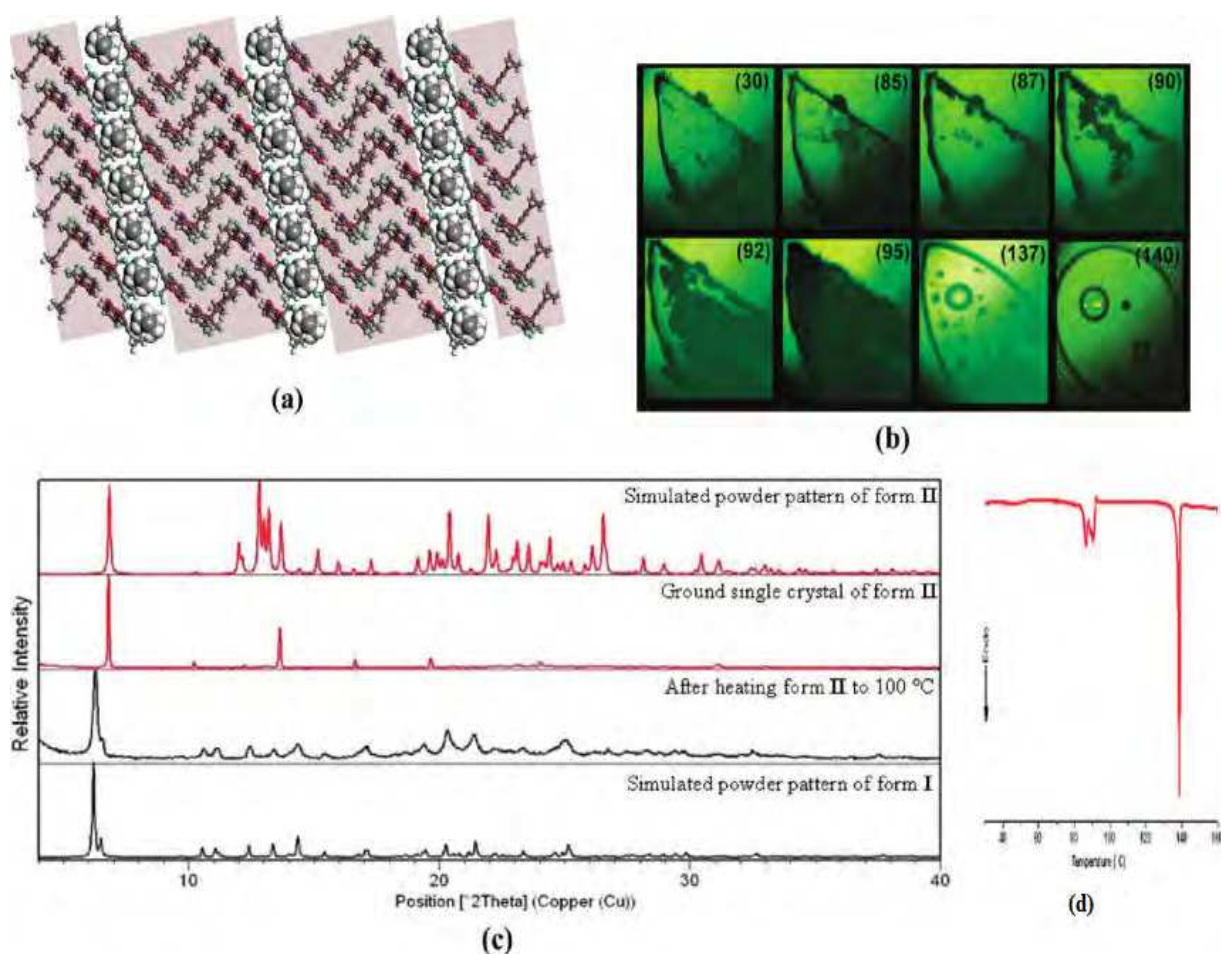


Fig. 8. (a) Crystal packing of efavirenz with the guest cyclohexane molecules represented in the space filling mode (b) HSM images of II (corresponding temperatures are given in parentheses) (c) PXRD patterns of forms I and II and the heated sample of form II (d) DSC plot for form II.

## 2.4 Lamivudine

Further studies on these categories of drugs have shown the existence of different crystal forms of lamivudine which is a nucleoside analog reverse transcriptase inhibitor. The solid state chemistry of this drug is of significant pharmaceutical interest as the drug is reported to exist in three crystalline forms. The two forms (Form I and II) reported in 1996 were again studied by Harris et al in 1997 (Jozwiakowski et al., 1996; Harris et al., 1997). Later in 2007, a new patent showing the existence of another polymorphic form III appeared (Singh et al., 2007). Michael et al have shown that Form I of lamivudine has been prepared by dissolving Form II in hot water and then adding an equal volume of methanol to reduce the solubility of lamivudine. The Form II has been obtained as a result of a synthetic process. The DSC studies showed heat mediated transformation of Form I to Form II. Besides this, these authors have also calculated the enthalpy of solution from solubility data and compared the results with experimentally determined enthalpy of solution by solution calorimetry technique. The enthalpy data revealed that the enthalpy of solution value agrees more closely in systems of low solubility than in system with high solubility.



Harris et al have recrystallized form I of lamivudine as needles from solutions in water, methanol or aqueous alcohols while form II as tetragonal bipyramids on slow recrystallization from dry ethanol and propanol or mixtures of ethanol and less polar organic solvents (Figure 9). Probably, the difference in the polarity of organic solvents led to two different crystalline forms. The authors have used cross-polarization magic angle spinning (CPMAS) NMR to differentiate the two forms. The Form II showed a simple spectrum indicating one molecule in the crystallographic asymmetric unit whereas the spectrum of Form I was found to be extremely complex due to differences in intermolecular packing environment or intramolecular geometry/conformation differences. These results were further confirmed by single crystal X-ray analysis. The Form II was bipyramidal crystals with one molecule in the asymmetric unit and Form I showed five molecules in the asymmetric unit of crystal lattice.

The crystals of Form III are obtained by subjecting the hot saturated solution of lamivudine in water to controlled cooling. The DSC and TGA showed this form to be different from Form I and II. The single crystal X-ray diffraction reveals it to be a hemihydrates with two molecules of water associated with four molecules of lamivudine in a crystal lattice.

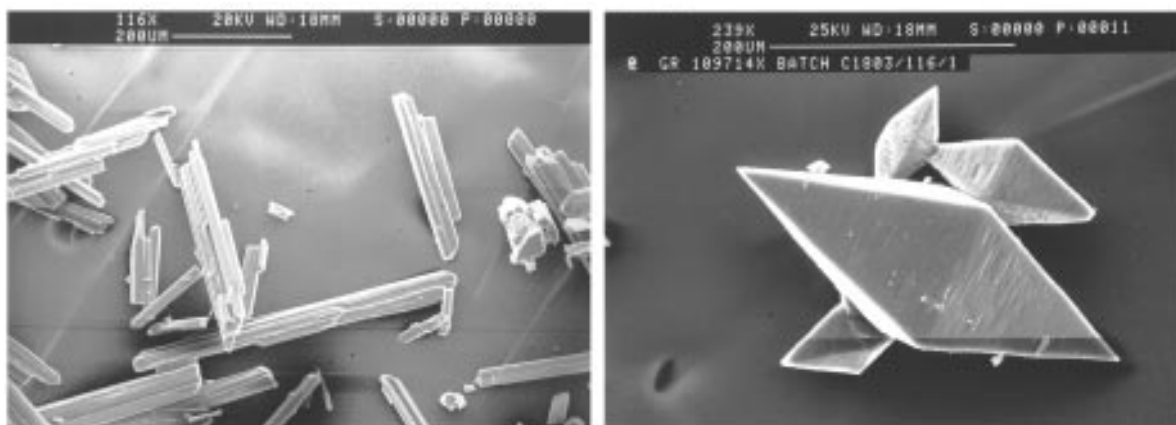


Fig. 9. Scanning electron micrographs of the two forms of Lamivudine

## 2.5 Stavudine

Stavudine, a thymidine nucleoside reverse transcriptase inhibitor, has been reported to exist in two anhydrous polymorphic forms and one hydrate. Harte et al and Guruskaya et al have reported the single crystal of Form I and Form II respectively (Harte et al., 1991 as cited in Gandhi et al., 2000; Guruskaya et al., 1991 as cited in Gandhi et al., 2000). However, the production of pure Form I is reported by Gandhi et al who have established the conditions of recrystallization governing the formation of this thermodynamically most stable form (Gandhi et al., 2000). The stavudine obtained during the synthesis process is recrystallized from hot organic solvents as the final step in the synthesis. The cooling of hot isopropanol solution from 80 to 70 °C for over an hour and then to 0-5 °C over 1.5 h yielded a mixture of Form I and II. However, Form I was found to be thermodynamically more stable. Therefore, some of the crystallization parameters such as rate of cooling or stirring were studied during recrystallization from isopropanol to selectively obtain Form I. After a lot of experimentation, it was found that slow cooling of hot isopropanol solution reproducibly yielded Form I. Kinetically both forms may be present initially but Form II redissolves and precipitates as Form I with slow cooling.

## 2.6 Cocrystals

Recently, cocrystallization has emerged as an attractive technique to recrystallize molecular solids that contain two or more distinct chemical components held together by non-covalent interactions. Anti-HIV agents have also been explored by this approach. The cocrystals of efavirenz with 4,4'-bipyridyl and 1,4-cyclohexanedione prepared by recrystallization of their grounded mixture from THF and from a mixture of n-heptane and THF respectively have been reported by Mahapatra et al (Mahapatra et al., 2010). Similarly, the multiple hydrogen bond donor and acceptor groups of lamivudine and zidovudine have been utilized by Bhatt et al for designing their cocrystals (Bhatt et al., 2009). These authors have designed zidovudine cocrystal using retrosynthetic approach where two drug molecules and one molecule of 2,4,6-triaminopyrimidine are held together by a three point synthon which forms basic part of their cocrystal structure (Figure 10).

Besides this, a cocrystal hydrate of lamivudine with zidovudine has been reported. Lamivudine and zidovudine molecules are expected to form synthon II with each other as shown in figure 11. However, during cocrystallization a hydrated 1:1 cocrystal is formed and the synthon formed is the extended IIA synthon rather than II. The observed synthon (IIA) is formed when a molecule of water intervenes in the hydrogen bond pattern of the synthon II. The cocrystallization without use of water resulted in no cocrystal formation in this case, perhaps due to the large repulsions between the carbonyl groups in the two API fragments (Figure 12).

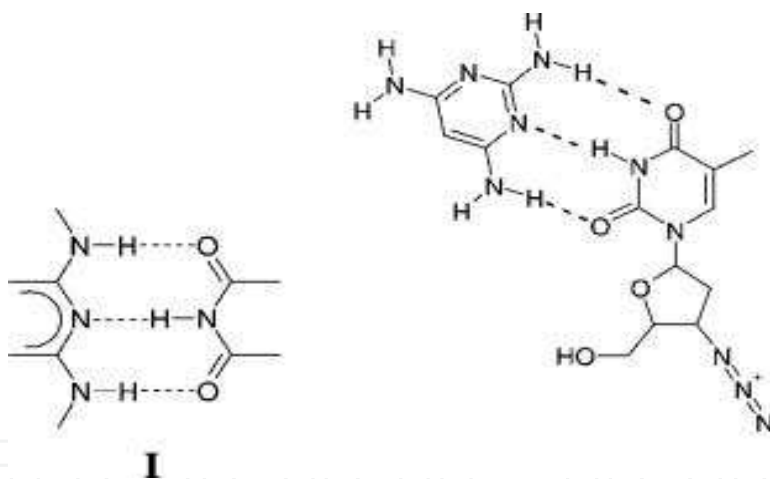


Fig. 10. Three-point synthon I and possibility of this synthon between zidovudine and 2,4,6-triaminopyrimidine

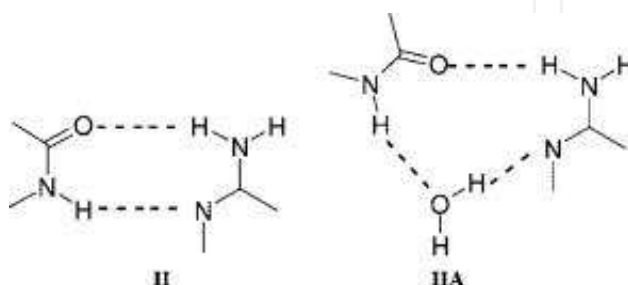


Fig. 11. Predicted two-point synthon II between lamivudine and zidovudine and observed synthon IIA in the hydrated co-crystal

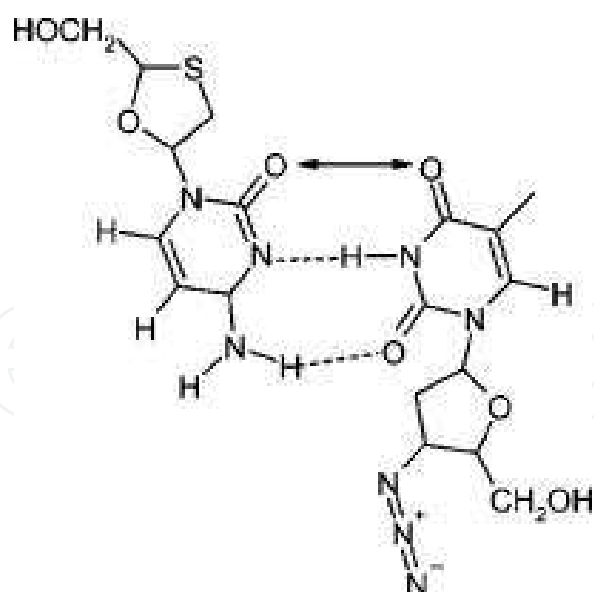


Fig. 12. Possible carbonyl - carbonyl repulsion in the putative lamivudine-zidovudine cocrystal with non-hydrated synthon II

Another cocrystal of lamivudine is designed and prepared with 3,5-dinitrosalicylic acid based upon synthon containing carboxylic acids and 2-aminopyridines. This cocrystal is an example of acid base interaction with a very complex hydrogen bond pattern. These authors also reported cocrystal of lamivudine with 4-quinolinone in a stoichiometry of 1:1. This cocrystal is stabilized by multiple  $N-H \cdots O$  and  $O-H \cdots O$  hydrogen bonds. This cocrystal is obtained during the screening process and is not based on any synthon theory. Thus the lamivudine-4-quinolinone cocrystal emphasizes the importance of cocrystal screening to obtain new cocrystals rather than completely depending on the synthon theory.



Fig. 13. Cocrystals of efavirenz and their preparation

The possible formation of cocrystals of efavirenz with 1,4-cyclohexanedione and 4,4'-bipyridyl was indicated by X-ray diffraction analysis (Mahapatra et al., 2010). The solids obtained from solvent drop grinding experiment, were subjected to recrystallization in particular solvent systems (Figure 13). Crystals of efavirenz-1,4-cyclohexanedione were obtained from heptane-THF solution. These crystals exhibited two symmetry independent dione molecules in a skewed conformation. One of these two dione molecules makes bifurcated  $N-H \cdots O/C-H \cdots O$  hydrogen bonds with two symmetry related molecules of efavirenz, forming a three molecular entity, while the other dione molecule makes linear chains with bifurcated  $C-H \cdots O$  hydrogen bonds. These two patterns stacked over one another to form grill-ribbon structure of the cocrystal (Figure 14).

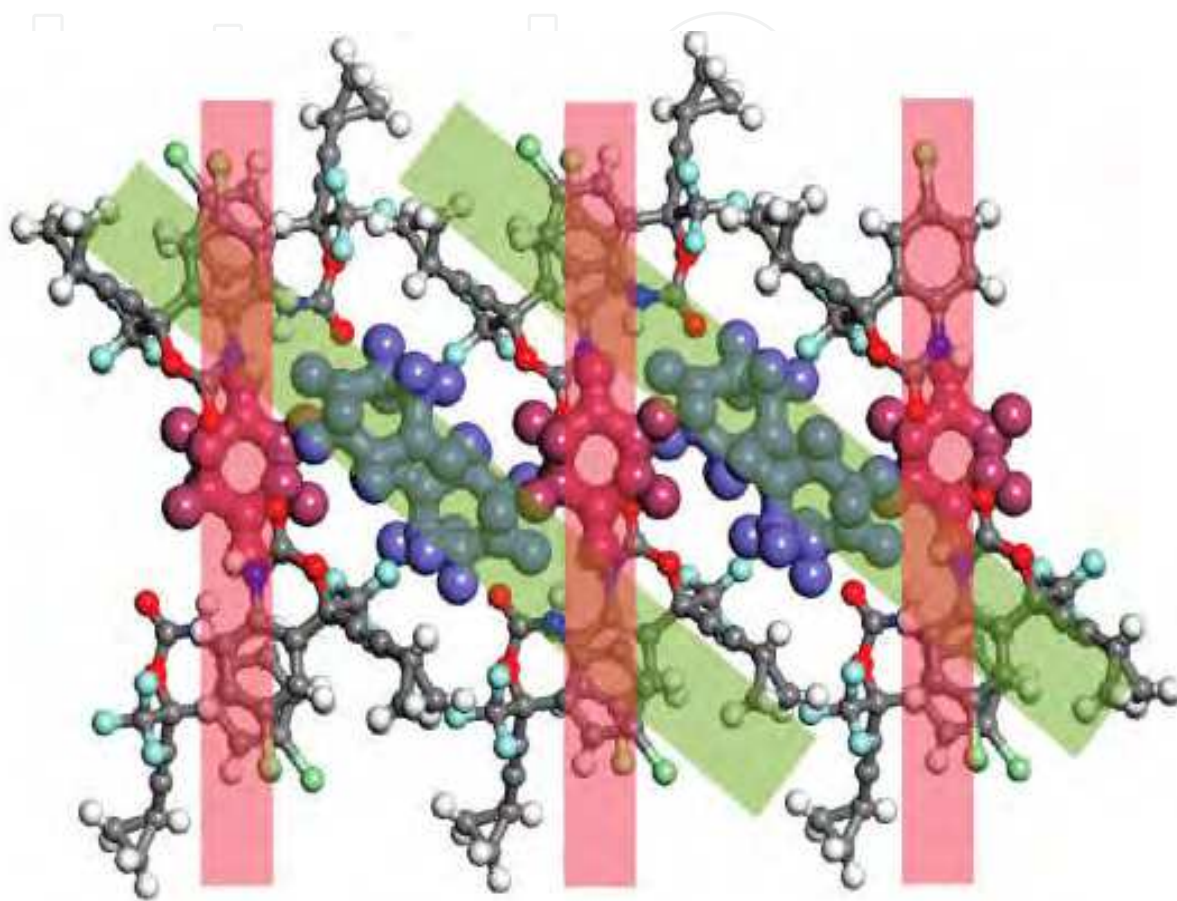


Fig. 14. Cocrystal of efavirenz and 1,4-cyclohexanedione: crystal packing along with the conformation in the native dione crystal (green).

The cocrystal of efavirenz with 4,4'-bipyridyl was obtained by recrystallization from acetonitrile. Unlike the cocrystal with cyclohexanedione in which the major synthon could not be anticipated, in this cocrystal two distinct heterosynthons were observed. While one of the efavirenz molecules interacted with bipyridyl through cyclic  $\text{N-H} \cdots \text{N}/\text{C-H} \cdots \text{O}$  hydrogen bonds, the other end of pyridine compound made a single point  $\text{N-H} \cdots \text{N}$  hydrogen bond with other molecule of efavirenz resulting in pillered assemblies separated by hydrophobic cyclopropyl residues (Figure 15).



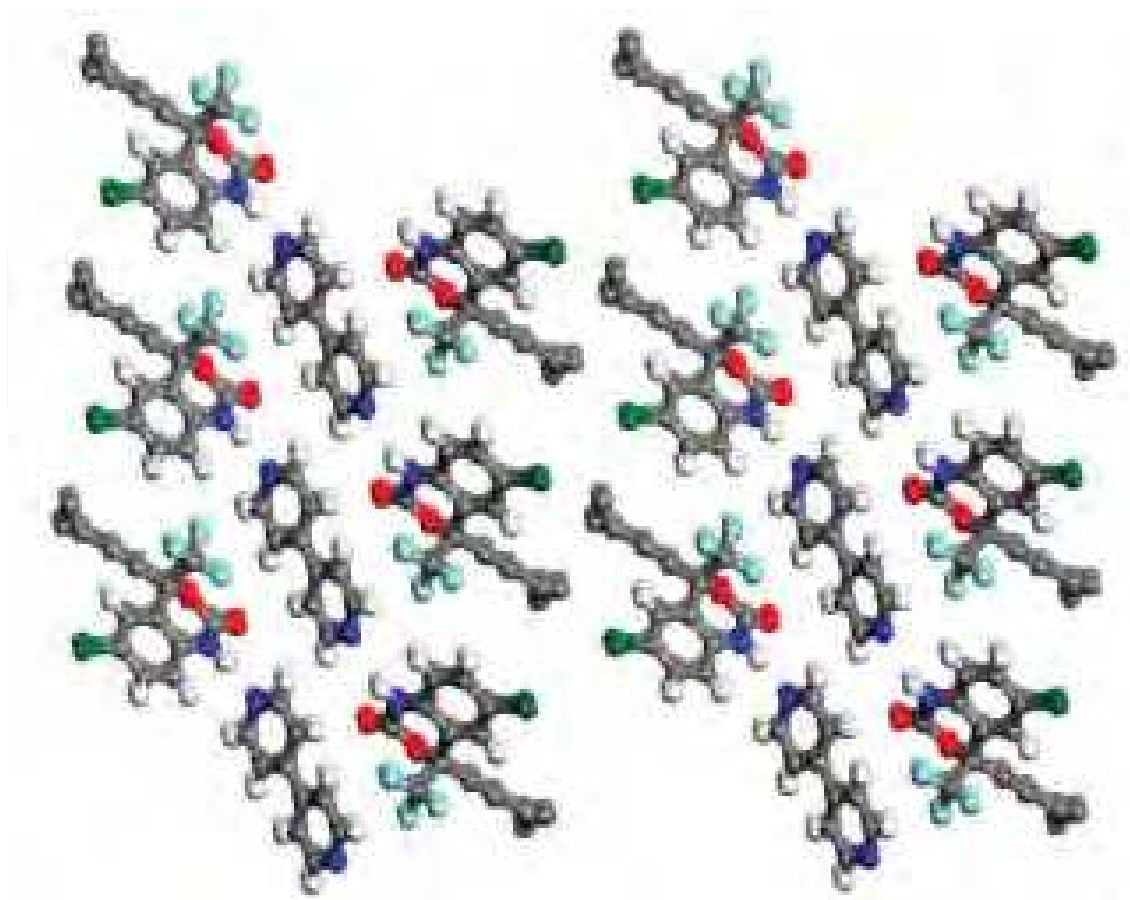


Fig. 15. Crystal packing of efavirenz- 4,4'-bipyridyl cocrystal

From the above examples it is clear that solvent recrystallization method has been the most common technique to prepare different crystal forms of a compound. However, with increasing demands to accelerate the process of crystal form identification, newer and advanced technologies need to be used as is exemplified by the isolation of three more polymorphic forms of ritonavir by high-throughput crystallization. In addition, cocrystallization technique has also been employing solution based crystallization methods to generate cocrystals of various pharmaceutical compounds. The studies on anti-HIV agents cited here are thus not simply academic exercises but have practical implications in preparation and identification of diverse crystalline forms of pharmaceutical material and can be of considerable benefit in formulation optimization.

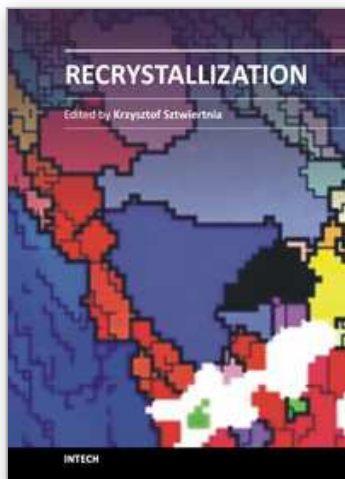
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Recrystallization shows selected results obtained during the last few years by scientists who work on recrystallization-related issues. These scientists offer their knowledge from the perspective of a range of scientific disciplines, such as geology and metallurgy. The authors emphasize that the progress in this particular field of science is possible today thanks to the coordinated action of many research groups that work in materials science, chemistry, physics, geology, and other sciences. Thus, it is possible to perform a comprehensive analysis of the scientific problem. The analysis starts from the selection of appropriate techniques and methods of characterization. It is then combined with the development of new tools in diagnostics, and it ends with modeling of phenomena.

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