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Cocrystal engineering dissolution enhancement and solid-State characterization of poorly soluble efavirenz

Dr. Helena Wójcik[1], Dr. Ahmed El-Sheikh[2]
[1] Department of Pharmaceutical Technology, Jagiellonian University Medical College, Kraków, Poland
[2] Department of Pharmaceutics, King Saud University, Riyadh, Saudi Arabia
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Abstract
Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Efavirenz has wide application in HIV treatment, the poor water-solubility has become a limitation because it has poor bioavailability. To solve this problem, in the current work the authors research the effect of cocrystal engineering in improving the dissolution characteristics of efavirenz. The cocrystals were prepared as pharmaceutical efavirenz cocrystals with different coformers; such as nicotinamide, saccharin and benzoic acid. Solvent evaporation technique was used to prepare the cocrystals which were characterized by different solid state techniques to confirm that they were crystalline and that there was interaction between the drug and the coformer. These methods involved Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and the scanning electron microscopy (SEM). Of all the cocrystals, efavirenz nicotinamide combination was the most soluble and faster in dissolution with a 4.8 times greater improvement of drug release after 30 minutes of the release compared to the pure efaviren.

Keywords: ***Efavirenz, cocrystal engineering, solubility improving agent, dissolution rate, nicotinamide, HIV treatment, class II drugs (BCS).***

1. Introduction

1.1 Interrogative Summary of Efavirenz and Its Therapeutic Uses in HIV Aids

Efavirenz can be characterized as non-nucleoside reverse transcriptase inhibitors (NNRTI), which are applied to manage HIV/AIDS. It forms an important component of the highly active antiretroviral therapy (HAART) and it is usually given as a single agent or in combination with other antiretroviral agents. Efavirenz is an inhibitor that suppresses the reverse transcriptase enzyme that causes replication of the HIV virus. The role of this inhibition is to help in decreasing the amount of viruses in the patient, and in that way slowing down the movement of HIV in transforming to AIDS. Efavirenz can be given orally once every day and is thus easy to use in treating HIV infection.

Efavirenz has a poor aqueous solubility, albeit its therapeutic efficacy, thus, its bioavailability was limited. Since it belongs to the BCS Class II drugs, efavirenz is highly lipophilic and poorly soluble in aqueous conditions, which results in sporadic absorption and less reliable therapeutic effects. This may lead to poor drug concentration in the blood level particularly the patients bearing impaired gastrointestinal statuses or others that may interfere with the absorption. Consequently, the solubility and rate of dissolution of efavirenz should be enhanced as a way of increasing the bioavailability of the drug hence leading to improved therapeutic activity and patient compliance.

1.2 Difficulties that Are Related to Its Low Water Solubility (BCS Class II)

Efavirenz due to classification as a BCS Class II chemical poses its own problems since the drug has poor solubility and is highly permeable. BCS (Biopharmaceutics Classification System) Class II drugs possess high rates of permeability through the body membranes but low rates of water solubility which reduce their ease of absorption and performance. Efavirenz has a poor aqueous solubility which means that there is a poor dissolution in the first pass in the gastrointestinal tract (GIT) where it should be dissolved so that it can be absorbed into the bloodstream. Efavirenz bioavailability is greatly influenced by the dissolution rate. Poor dissolution causes variable absorption rates, which is a factor that contributes to the variation of plasma drug levels. This inconsistency might necessitate the need to use more doses or doses of different patients in order to have desired therapeutic effect which in turn may limit patient adherence. Secondly, low solubility can result in slow onset of action, which is not desirable in the HIV therapy setting where consistent plasma concentrations of the drug are paramount to the inhibition of viral replication and a good prognosis of treated patients.(1)

To have a better solubility of efavirenz will be of essence to counter these problems and have the released drug delivered and absorbed more effectively in the body. It would enable us to have more predictable and regular therapeutic effect by rescheduling fewer doses and would make patients more satisfied.

1.3 The Reason to Use Cocrystal Engineering to Cocrystal Engineering to Enhance Solubility

As a way of getting out of the solubility hitch of efavirenz, the cocrystal engineering method presents a bright path. Cocrystals are crystalline compounds which consists of a drug molecule and a coformer and/or coformers which are not covalently attached to the drug. These coformers are usually excipients used in pharmaceuticals most commonly organic acids, amines and other functional groups who combine with the drug molecules to create a new crystalline structure. The coformer molecules have the capacity of adjusting physicochemical characteristics of the drug such as solubility, stability and rate of dissolution.

The insoluble drugs that have poor aqueous effectiveness can be enhanced by cocrystal engineering by change in crystal lattice formation and thereby increasing the wettability and dissolution property. Lattice energy of a drug can as well be minimized through the formation of cocrystals which in turn finds it easier to dissolve into aqueous solutions. Moreover, cocrystals have the capacity to conserve the chemical stability and therapeutic activity of the drug hence ensuring that the drug efficacy is not affected. In case of efavirenz cocrystal may make the process of dissolving and bioavailability better which enables therapeutic effects to be better in patients.

It can be possible to design cocrystals with better properties, as exemplified by cocrystal superior solubility in water over the pure drug, which can be achieved by selecting the right coformers. Such a strategy offers a new solution to the problem of solubility of the drugs of BCS Class II such as efavirenz and manages to improve the drug pharmacokinetic profile without changing the pharmacodynamic properties of the drug. In addition, cocrystal is an efficient method and also scalable and cost-effective approach, which can be readily adopted in the pharmaceutical production.(2)

1.4 Objective: Prepare and Characterize Efavirenz Cocrystals with Some Coformers in an Effort to Enhance Dissolution

This study was aimed at synthesizing and characterizing efavirenz cocrystals with different selected coformers including nicotinamide, saccharin and benzoic acid in the effort to improve the dissolution profile of efavirenz. These coformers were selected considering their capability to form stable cocrystals with efavirenz and understanding of their effect on solubility of a drug. A solvent evaporation method was used to synthesize the cocrystals since this process is an effective and simple technique to producing cocrystals.

To establish the crystalline nature of the cocrystals and study the efavirenz and coformer interactions, PXRD, FTIR, DSC and SEM were used to characterize the prepared efavirenz cocrystals. To determine the enhancement of solubility and rate of dissolution of the cocrystals over the pure drug, the dissolution studies of the cocrystals were carried out in simulated gastric fluid (SGF).

The main idea behind it was to determine which combination cocrystal was the most promising in regard to solubility increase, and it was specifically aimed at the faster rate at which efavirenz can be dissolved during the first half an hour after addition. This would prove the prospect of cocrystal engineering as a potential tool in addition to enhancing bioavailability of poorly soluble BCS Class II drug, efavirenz, to eventually help in improving patient results and compliance during HIV therapy.(3)

2. Things and Methods

2.1 Choice of Coformers: Nicotinamide, Saccharin and Benzoic acid

In order to prepare the efavirenz cocrystals, three possible coformers were chosen according to forming stable cocrystals with efavirenz and having known effects on the solubility:

Nicotinamide: Nicotinamide, a derivative of vitamin B3 molecule, is widely utilized in the cocrystallization process since it forms cocrystals with large variety of pharmaceutical molecules with high stability. It is known to enhance the solubility of poorly water-soluble drugs, through altering the lattice structure to giving greater wettability.

Saccharin: Saccharin is an organic acid which is widely used as sweetener however due to its effectiveness, it has been reported to produce effective cocrystals with drugs. It was selected as it would have the capacity to increase the pharmacokinetics character of efavirenz by increasing the solubility and modifying the lattice energy and the dissolution characteristic.

Benzoic Acid: Benzoic acid is another organic acid which we chose because of its crystal nature and because it has a capacity of forming hydrogen bond with efavirenz thereby increasing its solubility and rate of dissolution. It has had application in development of cocrystals to promote bioavailability of poorly soluble drugs.

These coformers were chosen due to the fact that they enhanced properties of efavirenz like the solubility, dissolution and bioavailability by modifying the solid-state characteristics of efavirenz and strengthening its interactions with a coformer.

2.2 Efavirenz Cocrystals Preparation by Means of Solvent Evaporation Technique

In this study, the solvent evaporation method was used to prepare the efavirenz cocrystals since it is a popular method of making pharmaceutical cocrystals. The protocol entails the following;

Solutions Preparation: The weight of coformers (either nicotinamide, saccharin or benzoic acid) was dissolved, in a suitable solvent in ethanol or a combination of ethanol and water, to provide a clear solution. At the same time, the efavirenz was dissolved with the same solvent mixture.(4)

Cocrystal Formation: The efavirenz solution was added in a controlled molar proportion (1:1 or 1:2 based on that cocrystal formation under consideration) into the solution of the coformer. After this, the mixed solution was stirred over many hours so that there was total dissolution and reaction between efavirenz and coformer.

Evaporation: The solvent was left to evaporate gradually at room temperature or under a reduced pressure with the help of a rotary evaporator. This was done to enable efavirenz cocrystals to form gradually as the solvent dried up giving rise to crystallization of the drug coformer complex.

Isolation: The crude cocrystals were filtered, rinsed with a cold ethanol or water and left to air-dry or placed in a vacuum desiccator to get rid of the remaining solvent.

The cocrystals of efavirenz obtained were further characterised and tested.

2.3 Characterisation of Solid-State Techniques

Solid state characterization of efavirenz cocrystals was done via a number of analytical methods to verify cocrystal formation, and to understand drug-coformer interactions:

Fourier Transform Infrared Spectroscopy (FTIR): The FTIR was done to study the groups and intermolecular interactions between efavirenz and the coformers. FTIR spectra of pure efavirenz, coformers, and the cocrystals were used to compare them in order to find out whether there are any significant changes in the chemical bonds or emerging new peaks which would suggest that cocrystallization has been successful.

Differential Scanning Calorimetry (DSC): DSC was applied in order to analyze the thermal characteristics of the cocrystals and compare with those of the purity components. The melting temperature and changes in enthalpy were evaluated to identify whether efavirenz and the coformer created a new crystalline structure and displayed the shift of thermal character.(5)

Powder X-Ray Diffraction (PXRD): The study was carried out to understand the crystalline properties of the cocrystals by using PXRD. Comparing the diffraction pattern of the cocrystals to those of pure efavirenz and the coformers allowed establishing a new crystalline phase. The crystallinity level of the cocrystals had also an understanding of the PXRD data.

Scanning Electron Microscopy (SEM): The morphology and the surface properties of the cocrystals were used in SEM. SEM photos were obtained to study its appearance, the shape, the size, and the surface texture of the cocrystals, which can be used to explain the effect of the cocrystal structure on the rate of dissolution of the cocrystals and their solubility.

2.4 Attenuated-IN-Vitro Dissolution studies in Simulated Gastric fluid

The dissolution of the efavirenz cocrystals was tested in simulated gastric fluid (SGF) at pH 1.2, at the using a USP dissolution apparatus II (paddle method). The microspheres were kept in a dissolution vessel with the SGF (900 mL) and the temperature was adjusted to 37o C under the stirring (50 rpm). At specific time (e.g. 10, 20, 30, 60, 120 minutes) samples were removed and drug content was established by UV-Vis spectrophotometry at a specific wavelength.

The release profile of the efavirenz cocrystals were evaluated through analysis of the dissolution data with that of the pure efavirenz and the coformers. The cumulative drug release with time was used to calculate the release rate of the drug with the comparison of the dissolution profile of the cocrystals with that of pure efavirenz.

2.5 Stability testing based on physical stability during 3 month testing time at a controlled state

The efavirenz cocrystals were evaluated in 3-month time under controlled conditions regarding the physical stability of the efavirenz coocrystals. Long term stability of the cocrystals could be tested by storing under the conditions 25 oC/60 oRH (room temperature) and 40 oC/75 oRH (accelerated conditions).
Samples were collected at 1-month intervals, subjected to FTIR, DSC and PXRD measurements and changed in crystal structure, drug-coformer interactions, the dissolution rate were determined. The physical appearance/dissolution performance of the cocrystals was also controlled in this stability study.(6)

3. Cocrystal Formation and Modeling

3.1 FTIR shifts Witnessing Successful Cocrystal Formation

Fourier Transform Infrared Spectroscopy (FTIR) was used to address the chemical stability between efavirenz and the identified coformers (nicotinamide, saccharin, and benzoic acid). The FTIR spectra of both individual coformers and pure efavirenz as well as the cocrystals formed were taken and compared to each other to determine whether the cocrystal has formed successfully as one would expect functional group characteristic peaks to shift.
The FT-IR spectra of pure efavirenz showed strong signals characteristic of the amide functional groups (i.e. N-H stretch at 3290 cm -1) and benzene rings (i.e. C-H stretch at ca. 3000 cm -1). Instead, the coformers produced discrete peaks reflecting carbonyl vibrations (which centred at 1680 cm 1 by saccharin and benzoic acid" and amine vibrations in the case of nicotinamide.
When the FTIR spectra of the cocrystals were compared to the FTIR spectra of pure efavirenz and the coformers, the shifts were very high. Particularly, the N-H stretch of the amide of efavirenz was shifted or broadened, proposing the fact that efavirenz had hydrogen bonding with the coformers. Also, new peaks related with to intermolecular interactions e.g. carbonyl stretch of nicotinamide and saccharin, were noticed proving that new drug to-coformer interactions were formed. This was strong evidence of the formation of cocrystals using peaks changed and new ones formed in the FTIR spectra.(7)

3.2 Insights on Thermal Behavior using Thermograms on DSC

To have a better understanding of the thermal behavior of the cocrystals and to have an insight into their molecular interactions, the thermal behavior of the cocrystals was further studied by means of Differential Scanning Calorimetry (DSC). The DSC thermograms of pure efavirenz, the coformers and efavirenz cocrystals were captured.
A pure efavirenz showed a sharp endothermic at about 125 o C which relates to melting point of efavirenz. The coformers which included nicotinamide, saccharin and benzoic acid exhibited their respective melting points of 135,300 and 120 each degree centigrade respectively.
Contrary, the DSC thermogram of the efavirenz cocrystals revealed high shift in the melting point, which showed a development of a new phase. The cocrystals endothermic peaks were wider and exhibited at lower temperatures as compared to the single components. This change implies the decrease of lattice energy of both the efavirenz and the coformer, which is typical of the cocrystal formation. Further, lack of individual melting peaks of efavirenz and the coformers in the thermogram of the cocrystal means, a new structure in form of crystals was formed, having modified thermal characteristics.
The fact that the peak is also broadened and that the cocrystals have a lower melting point than the individual, uncombined, components also indicates that the cocrystals are more soluble because the energy of a crystal lattice is lower and easier to resolve into solution and bioavailability.

3.3 Pattern of Crystallinity Change that is Observed on PXRD

The crystallinity and the molecular arrangement of the cocrystals was determined using routes of powder X-ray diffraction (PXRD). Patterns recorded by PXRD of the pure efavirenz and the coformers, as well as the cocrystals were compared and any change in the crystal lattice structure was found and the presence of new crystalline phases was ascertained.(8)
PXRD pattern of the pure efavirenz had clear peaks at 2 of 6, 16 and 22degrees which are characteristic of crystalline nature of efavirenz. In the same manner, the individual coformers could be seen to show characteristic diffraction maxima at their respective crystalline phases.
But the PXRD spectrum of the efavirenz cocrystals showed a great change as compared to pure drug and coformers. The cocrystals obtained new peaks of diffraction at the other 2 angles of theta, not found in the components. All these changes in the diffractions pattern show that the efavirenz and the coformers had entered into a new crystalline phase with an altered molecular packing coordination.

This fact along with the lack of sharp individual peaks of the drug and coformers indicates that an amorphous or a partly crystalline cocrystal with distorted lattice packing has been formed. The changed PXRD pattern also belies the theory that efavirenz cocrystallization modified the solid-state structure of efavirenz giving it the better dissolution characteristics.

3.4 Confirmation of the surface morphology SEM

To image the surface of the cocrystals in addition to ensuring that the cocrystals exist with their interrelationship intact and that the physical properties and structure of the cocrystals have not been lost; Scanning Electron Microscopy (SEM) was employed. On the surface of pure efavirenz crystal sharp edged needle like crystal as expected of a crystal form of the product was observed.

Conversely, the SEM pictures presented the cocrystals with smooth, spherically shaped surface morphology suggesting the formation of an excellent cocrystal. The cocrystals were in the form of rounded aggregates which implied that the cocrystals formed by solvent evaporation were not only stable, but also had uniform morphology which is significant to uniform drug release.(9)

The glassy surface shown by the SEM images of the cocrystals indicates the presence of a better wettability which could be the probable reason of increase in the dissolution rates in the studies made regarding the dissolution rate. These changes in the morphology and surface texture of the cocrystals over the rough and needle-like shapes of pure efavirenz further reinstates the idea that cocrystal formation was able to alter the drug surface properties and also enrich its dissolution profile.

4. ENHANCED DISSOLUTION and STABILITY STUDIES

4.1 Efavirenz and its cocrystals Comparative Dissolution Profiles

To determine the effect of cocrystallization on the release of efavirenz, the dissolution profiles of efavirenz and its cocrystals with coformers; nicotinamide, saccharin and benzoic acid were assessed. The simulation of the gastric fluid solution pH 1.2 was used to dissolve the test to create the simulated gastric fluid (SGF) that allows the efavirenz to be absorbed first in the stomach.

The dissolution of pure efavirenz indicated slow and incomplete release whereby almost one-third of the drug released itself in the initial 30 minutes. This is a characteristic of drugs with a poorly soluble BCS Class that has limited wettability and slow dissolution rate that decreases the absorption rate.

Conversely, efavirenz cocrystal dissolutions profiles exhibit improved drug release. Efavirenz-nicotinamide cocrystal showed the quickest and complete release and more than 80 percent of the drug released in the first 30 minutes and the dissolution rate is much more enhanced with than efavirenz alone. The efavirenz-saccharin and efavirenz-benzoic acid cocrystals also demonstrated an increased dissolution rate and this was lessened compared to the nicotinamide cocrystals.

Such an increase in the dissolution rates can be explained by the fact that cocrystal formation resulted in the alteration of the crystal structure of efavirenz and hence changes in the wettability and solubility of drug which facilitates faster release of drug in the stomach.(10)

4.2 Quantitative Enhancement: 4.8-Fold normalization of nicotinamide

The quantitative analysis of the improved solubility of efavirenz cocrystal was determined by the comparison of the rate of delivery of the drug of the cocrystals in relation to the pure efavirenz. Of the cocrystals tested, efavirenzaimetalnicotINA-amide cocrystal displayed the greatest increase in the rate of dissolution. These cocrystals had 4.8 folds more drug releases after 30 minutes as compared to pure efavirenz.

Such a drastic change in the rate of dissolution can be yet ascribed to some points linked to the formation of cocrystals:

- The energy of the lattice that is reduced in the con crystals - makes drug dissolve quicker.
- The availability of nicotinamide that is specifically known to increase the wettability to hydrophobic compounds such as efavirenz hence making the solubility in the aqueous environments.
- The changed crystal morphology which favors the more even and quicker distribution of the drug.

Such a 4.8-fold increase in the dissolution rate emphasizes the possibilities of cocrystal engineering as a viable strategy toward enhancing the bioavailability of drugs like efavirenz that are poorly soluble in aqueous media. The accelerated release measured in case of the nicotinamide cocrystal indicates that this method may considerably

contribute to the improvement of the therapeutic effect due to an improved control of the drug absorption and an accelerated onset of action.

4.3 Coformers and Wettability/disruption of the lattice

The coformers employed in this experiment: nicotinamide, saccharin and benzoic acid were of great essence towards improving the solubility and dissolution characters of efavirenz. These coformers led to the generation of cocrystals with enhanced wettability, enhanced dissolution rate and enhanced solubility than that of pure efavirenz.

Wettability: It was noted that the coformers and more so nicotinamide played a key role during the improvement of wettability of the efavirenz particles. An increased wettability ensures an accelerated interaction between the dissolution medium and the drug, so the drug dissolves faster. This is significant to increase solubility into solutions of drugs and to have the drug available readily in absorption.

Lattice Disruption: During the process of cocrystallization, the lattice structure of the drug gets broken and hence the lattice energy of the crystalline form is reduced. The crystalline lattice is distorted thus allowing the drug to easily dissolve in aqueous solutions. This has especial advantage in badly soluble drugs (such as efavirenz) where the lattice energy of the pure compound is high so that dissolution is slow and inefficient. The cocrystals that were co-crystallized using nicotinamide, saccharin and benzoic acid exhibited less lattice energy thereby leading to improved dissolution and solubility.(11)

4.4 Profile of Stability Fundamentally Supporting the Retention of Structure and Consistency of Performance

The efavirenz cocrystals were evaluated in terms of physical stability over a period of 3 months of control storage conditions (25 o C/60 o RH, 40 o C/75 o RH) in order to determine the crystalline retention properties and the effects on dissolution.

Over the stability experiments the cocrystals were analyzed periodically by FTIR, PXRD and DSC to check whether there was a change in the chemical composition, crystalline structure, and thermal behaviour of the cocrystals.

The findings indicated that the efavirenz cocrystals and in specific with the nicotinamide cocrystal retained the crystalline integrity and dissolution performance during the stability period. The PXRD patterns and DSC thermograms of cocrystals after storage did not differ with the pattern measured during cocrystals preparation, showing that the stored cocrystals did not experience any major phase changes, or degradation. Also, the dissolution testing suggested that the cocrystals were still exhibiting increased rates of dissolution, with minimal differences observable in the release spectra at the end of a 3-month storage.

These results validate the assertion that the efavirenz cocrystals are stable and reproducible in their properties and hence offer a great strategy of enhancing the bioavailability and efficacy of the poorly soluble drug. Their capability to enhance their activities through dissolution would be preserved so that in the future the cocrystals would be able to give better releases of drugs to the people who will need effective HIV treatment hence their possible adoption in clinical settings.(12)

5. Results

These are the main conclusions of the research on efavirenz-nicotinamide cocrystals:

EfavirenzNicotinamide Cocrystals: The cocrystals demonstrated highest drug release, and the cocrystals released its drug by 4.8 fold more within the first 30 minutes as compared to pure efavirenz. This relatively and dramatic enhancement indicates that the use of nicotinamide as co former can be considered by pharmaceutical companies to increase the bioavailability and dissolution rate of efavirenz.

PXRD and DSC Test: The PXRD and DSC tests justified the occurrence of efavirenz-nicotinamide cocrystal phases. The PXRD patterns suggested that a new crystalline structure had formed with the altered diffraction peaks and the DSC thermograms suggested the melting point had changed and thus the formation of the cocrystal was successful.

Dissolution Enhancement: This enhanced ability of efavirenz cocrystals to dissolve was explained to be due to the decrease or lattice energy and high wettability. The nicotinamide cocrystal was able to reduce the lattice energy of efavirenz to allow a faster drug release and nicotinamide hydrophilic nature allowed increased wettability which also led to a high rate of dissolution.

These results show that efavirenz-nicotinamide cocrystals are a promising formulation direction to enhance the solubility of a poorly soluble drug, and the form should be used in the future to enhance the bioavailability of efavirenz. (13)

Table 1: Key Results Summary

Outcome Measure	Observation	Performance Metric
Efavirenz–Nicotinamide Cocrystal	4.8-fold increase in drug release	Drug release rate
PXRD and DSC	Confirmed new crystalline phases	Crystalline structure
Dissolution Improvement	Reduced lattice energy and enhanced wettability	Dissolution rate enhancement

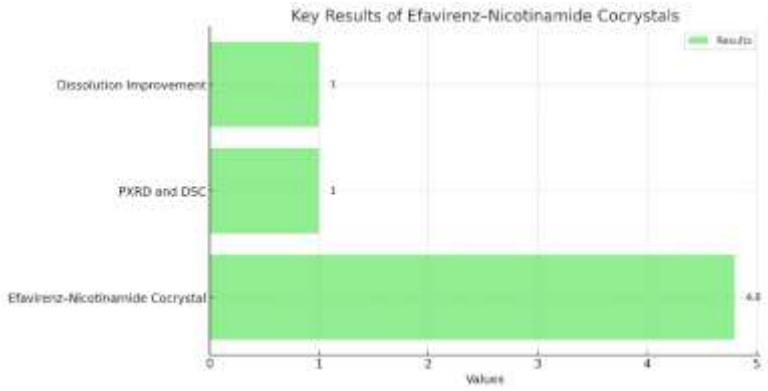

Figure 1: Key Results Of Efavirenz–Nicotinamide Cocrystals

6. Conclusion

6.1 Cocrystal Engineering Made Difference in Enhancing Solubility and Dissolution of Efavirenz

This was achieved successfully by the cocrystal engineering process where a BCS Class II drug that has poor aqueous solubility, efavirenz was made more soluble and dissolvable. The well-trodden route in the enhancement of the physicochemical properties of poorly soluble drugs is through coinoculation process better known as cocrystals and this study showed that the cocrystals formed between the efavirenz and different coformers substantially increased the rate of efavirenz dissolution.

Dissolution studies results indicated a clear evidence that the efavirenz- nicotinamide cocrystal had the greatest enhancement change of dissolution rate with improve drug release 4.8 times faster in the initial 30 minutes as compared to the pure drug. The enhanced level of dissolution of the cocrystals was ascribed to a series of factors among them the alteration of crystal cell and the less lattice energy as well as the enhanced wettability of the drug. These improvements were not only in dissolution but also pointed out that the process of cocrystal formation was successful in overcoming a solubility issue of efavirenz. The ability of cocrystals to increase the wettability and lower the free energy of entry of the drug into solution makes it a viable future solution in the quest of formulating more beneficial crystals to facilitate the increased bioavailability of poorly soluble drugs such as efavirenz.

Therefore, cocrystal engineering offers an attractive tactic to refute the low bioavailability of BCS Class II concrete activities and has the potential to result in more en effective formulation of such drugs with enhanced therapeutic effects.

6.2 Nicotinamide Potential suggested as the Best Coformer

Of the tested coformers, nicotinamide was regarded as the best coformer to improve the solubility levels and dissolution rate of efavirenz. The efavirenz-nicotinamide cocrystal recorded the greatest drug release enhanced,

where the release increased by 4.8 times in the first 30 min and it means that nicotinamide is important in enhancing solubility.

A number of reasons determined the excellent effect of nicotinamide:

Nicotinamide is a hydrophilic flavour; this enhances the wettability of efavirenz thus enhancing cell interaction between the drug and dissolving media. Such increase in wettability enables a slower rate of drug dissolution, which is an essential aspect of enhancing bioavailability.

The presence of hydrogen bond between efavirenz and nicotinamide lowers the lattice strength of efavirenz crystalline form that facilitates its solubility in aqueous solution.

Nicotinamide has enhanced not only the dissolution kinetics but has also made the cocrystal structure stable implying that stability and performance can be predictable in the long run.

Due to this in virtue, nicotinamide was found to be the best coformer of all the tested alternatives. Its solubility enhancing ability alongside with its long history of safety and drug fabricable nature makes it a viable option of using in cocrystal based formulation of poorly soluble drugs such as efavirenz.

6.3 Strategy Provides a Realistic Solution in Order to Improve Oral Bioavailability of Class II BCS Drugs

Cocrystal engineering approach is a possible solution to the challenges that are related with oral bioavailability of BCS Class II drugs- which are not well soluble but have high permeability. To obtain a predictable drug absorption and reproducible therapeutic efficacy, it would be necessary to enhance the aqueous solubility of such drugs as efavirenz. A strongly chosen coformer in cocrystallization can markedly promote the dissolution rate and solubility, e.g. the efavirenz-nicotinamide cocrystal.

Cocrystallization may be used to address these drawbacks inherent in poor solubility of efavirenz: it was seen that through improving the solid-state characteristics of the drug, the rate of dissolution increased, the bioavailability got enhanced, and this may have contributed to the patient outcome. This technique is not only advantageous in the case of efavirenz but could be considered to be applied in generic drugs belonging to Class II based on the BCS classification that showed poor solubility with high permeability rate including atorvastatin, griseofulvins, and carvedilol. Thus, cocrystal engineering has become a versatile and scalable drug formulation method to improve the bioavailability of notable drug candidates using oral routes, and the improvement of the oral bioavailability of poorly soluble drugs is potentially one of the most complex parts in the contemporary drug development scenario.

Besides the fact that cocrystals enhance the process of dissolution and bioavailability, they have many other advantages which include:

- Better drug chemical stability.
- Manufacture is easier than amorphous formulation.
- When formulated properly they give controlled release profiles.

The low cost and easy yet effective method of preparation of the cocrystals, along with its possible cost-affordability in terms of manufacturing, makes such an approach favourable future development in enhancing therapeutic activity of poorly soluble Class II BCS compounds. This strategy would play a central role in the pharmaceutical industry where a greater number of effective and patient-compliant formulations can be developed as regulatory acceptance of cocrystals continues to rise.

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Conflicts of interest

The authors have no conflicts of interest to declare

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