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Review Article

A Review on Pharmaceutical Cocrystals of Luliconazole for Solubility Enhancement

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Abstract:
Poor aqueous solubility is still a major issue in the development of many pharmaceutical drugs, especially those comes under the BCS Class II. Luliconazole is one such antifungal drug. It shows good permeability, but its low solubility often limits how effectively it works in therapy. Because of this, improving its solubility becomes quite important from a formulation point of view. Luliconazole is a potent imidazole class antifungal drug used in treatment of fungal infections such as superficial mycoses. But its poor solubility makes its clinical performance less effective. Therefore, in recent years pharmaceutical cocrystallization has been innovated by the researchers to enhance the activity of luliconazole. This review focuses on the basic principles of pharmaceutical cocrystals including their formation, different methods of preparation, and their role in enhancing drug performance. Thus, recent studies (2022–2026) have shown that advanced delivery systems such as nanosuspensions, nanoemulsions, and vesicular carriers significantly enhance the solubility and antifungal efficacy of luliconazole. The fumaric acid cocrystals has been explored to overcome this limitation of luliconazole. With studies reporting up to 12-fold increase in solubility and more than 90% drug release in optimized formulations. They also help in improving solubility, dissolution rate & hence increasing bioavailability & its efficacy. Overall, the formulation of luliconazole fumaric acid cocrystal offers improved performance & outcome in treatment of superficial mycoses and other fungal infections.
Keywords: Luliconazole, Cocrystals, Solubility enhancement, Coformers.

Introduction

Fungal infections are among the most common health concerns in the community, especially affecting individuals who have weakened immune systems such as patients with HIV or tuberculosis. Superficial mycoses, which involve the skin, hair, and nails, are commonly treated using antifungal agents like luliconazole.[1] Luliconazole is an imidazole class antifungal agent with broad-spectrum activity against dermatophytes and yeasts [2] it is widely used in the treatment of various fungal infections. [3] One of the major limitations comes with luliconazole is its poor aqueous solubility, which causes a reduced dissolution rate and affects its therapeutic efficacy. Solubility plays an important role in determining

drug absorption and overall bioavailability, making it a key parameter in formulation development.

To overcome these limitations of luliconazole, pharmaceutical cocrystal technology is used that offers a promising approach.[4] Pharmaceutical cocrystals are crystalline systems that are composed of an active pharmaceutical ingredient and a suitable coformer in a definite stoichiometric ratio, and they are held together by non-covalent interactions such as hydrogen bonding. This process involves the formation of a crystalline complex between the active pharmaceutical ingredient and coformer such as Fumaric acid, this approach enhances the solubility and dissolution of the drug without affecting its chemical structure.[5] It has been reported that approx. 40% of marketed drugs and nearly 60% of newly developed drugs have the problem of poor aqueous solubility. This issue is mainly occurring due to the increasing molecular size and lipophilicity of modern drug molecules, which makes their dissolution in aqueous fluids challenging. Poor solubility often results in decrease in bioavailability. Various formulation strategies have been investigated to overcome the limitations of luliconazole. For instance, Saldanha et al. reported improved drug release and antifungal activity using a nanosuspension-based gel, while Patidar et al. demonstrated enhanced skin permeation through niosomal systems. Similarly, Solanki et al. developed a nanoemulsion-based gel that significantly improved drug diffusion and bioavailability. [27][28] These approaches highlight the effectiveness of advanced delivery systems; however, they often involve complex formulation techniques and stability concerns. Therefore, there is a need for simpler and efficient approaches such as pharmaceutical cocrystallization. [6]

The formation of cocrystals involves non-covalent interactions between the drug molecule and coformer. These interactions help in improving the physicochemical properties of the drug, majorly its solubility and dissolution rate**.** Therefore, the present study focuses on the formulation and evaluation of luliconazole cocrystals to enhance its solubility and dissolution characteristics.

Rational of the Study

One of the most common problems occur during drug development is poor aqueous solubility of the drugs, especially in drugs that comes under the BCS Class II. Luliconazole is a well-known antifungal agent, but its low solubility reduces its proper dissolution and overall effectiveness in treatment. Because of this, it is important to evaluate the approaches that can improve its solubility without changing its original therapeutic action.[7]

In recent years, cocrystallization is widely used technique to improve the physicochemical properties of drugs. Still, not much focused work is available on improving the solubility of luliconazole using this approach.[8] So, this study is mainly carried out to form cocrystals with a suitable coformer, such as Fumaric acid that help in enhancing the solubility and dissolution properties of luliconazole, also this further improve its overall performance.

Advanced Drug Delivery Approaches for Luliconazole

Luliconazole is a poorly water-soluble antifungal drug, which limits its therapeutic effectiveness due to low dissolution and poor skin penetration. To overcome these limitations, various advanced drug delivery systems have been explored in recent years.

For instance, Saldanha et al. developed a nanosuspension-based gel with improved drug release and antifungal activity, while Patidar et al. reported enhanced permeation and efficacy using niosomal gel systems. [28] [29]

Nano-based formulations have shown significant potential in improving solubility and bioavailability. Solanki et al. developed a nanoemulsion-based gel with improved drug diffusion, whereas Giri et al. reported a microemulgel system achieving around 94% drug release over 24 hours. In addition, advanced carrier systems such as nanofibers and

nanoparticles have also been investigated. Nimhan et al. demonstrated sustained drug release using nanofiber patches, while Rani et al. reported nearly 12-fold enhancement in solubility using mesoporous silica nanoparticles. Similarly, Singh and Narang developed polymeric micelle hydrogels with improved drug penetration and antifungal activity.[30] [31]

Despite these advancements, such systems mainly involve complex formulation processes and stability challenges. Therefore, there is a need for simpler and more efficient approaches like pharmaceutical cocrystallization has a promising strategy for improving the solubility and dissolution of poorly soluble drugs like luliconazole.

Factors Affecting Drug Solubility

The solubility of a drug is influenced by several physicochemical factors that determine how effectively the drug can dissolve in a given solvent. The most important factors are the strength of the crystal lattice. Drugs which contain tightly packed crystal structure have strong intermolecular forces, which make drugs lattice stronger and solvent molecules have difficulty to break that lattice and dissolve the drug. This is why such compounds generally shows less aqueous solubility.[11] The presence of hydrophobic groups in the molecules structure also decreases solubility, because they have low aqueous solubility.[12] They are very common in lipophilic drugs such as Luliconazole, where poor water solubility becomes a major limitation during formulation development.

Pharmaceutical Cocrystals

Pharmaceutical cocrystals are solid crystalline systems which are composed of active pharmaceutical ingredient that is combined with a compatible coformer in a stoichiometric ratio within a single crystal lattice.

Cocrystallization has been widely explored as an effective strategy to enhance solubility of poorly soluble drugs. Ouyang et al. reported that cocrystal formation improves solubility and dissolution without altering the chemical structure. Similarly, Gowda et al. demonstrated enhanced solubility and dissolution in efavirenz cocrystals, while Ahirrao et al. (2022) reported faster dissolution rates in etodolac cocrystals prepared using GRAS coformers. These findings clearly indicate the potential of cocrystal engineering in improving drug performance.

The components of cocrystals are associated through non-covalent interactions, mainly hydrogen bonding, along with weaker forces such as van der Waals interactions.

In salt formation, cocrystals do not transfer protons between the interacting species. This feature of cocrystal makes them suitable for a broader range of drug molecules, including those that are weakly ionizable or completely non-ionizable. [9]

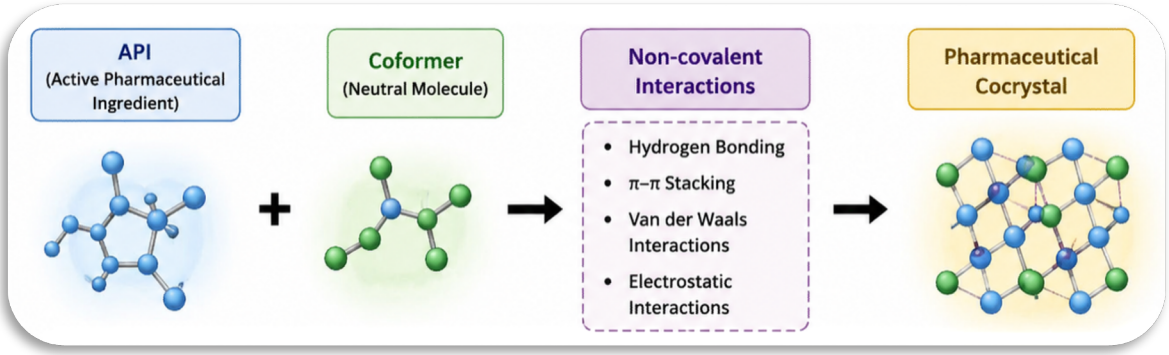

Figure 1: Formation of Pharmaceutical Cocrystals

Figure 1 illustrates the process of cocrystal formation through intermolecular interactions between the drug and coformer.

In these systems, the drug is paired with a suitable coformer that is selected on the basis of its safety profile and ability to form stable interactions between molecules. For example, Luliconazole can be combined with coformers such as Fumaric acid to generate stable crystalline complexes.[10] The choice of coformer is critical, because it affects the molecules arrangement within the crystal and also it affects the physicochemical characteristics of the resulting cocrystal. By changing its intermolecular forces, cocrystals can change their properties such as solubility and dissolution behavior.

Therefore, pharmaceutical cocrystals are one of the practical and innovative strategy for overcoming solubility-related problems in drug development. To better understand the advantages of cocrystals over other solubility enhancement techniques, a comparison is presented in Table 1.

Table 1: Comparison of Cocrystals with Other Solubility Enhancement Techniques

Parameters	Cocrystals	Salt Formation	Solid Dispersion
Chemical Change	No	Yes	No
Stability	High	Moderate	Low
Suitable for	High	High	Moderate
Stability Improvement	Non-ionizable drugs	Ionizable drugs	Poorly soluble drugs
Complexity	Moderate	Low	High

Mechanism of Solubility Enhancement

The enhancement in solubility through cocrystal formation mainly happens because of changes in the internal arrangement of the drug molecules. In its pure form, a drug generally exists in a tightly packed crystal structure where strong intermolecular forces hold the molecules together. Due to this strong packing, solvent molecules find it difficult to enter the lattice and dissolve the drug efficiently.

When a cocrystal is formed, this arrangement does not remain the same. The drug molecule starts interacting with a coformer, and this leads to the formation of a new crystal structure.[13] These interactions are mostly non-covalent in nature, especially hydrogen bonding. Because of this, the strong drug–drug interactions are partially replaced by comparatively weaker drug–coformer interactions. As a result, the overall crystal lattice becomes less rigid, which makes it easier for the solvent to break it and dissolve the drug.

The presence of a coformer can change the packing pattern and surface properties of the crystal. In some cases, this improves the wettability of the drug particles which helps the solvent to spread more easily over the surface. This also contributes to increased dissolution. Also, if the coformer has good solubility, it can also participate in the solvation process and further improve the overall solubility of the system.[14]

In addition to this, both thermodynamic and kinetic properties are affected. A reduction in lattice energy improves the equilibrium solubility, while better surface interaction with the solvent enhances the dissolution rate.[15]

Because of all these combined effects, cocrystallization is considered as a useful and practical approach to improve the solubility and bioavailability of poorly soluble drugs such as Luliconazole.

These improvements are mainly attributed to intermolecular interactions such as hydrogen bonding and crystal lattice modification, as reported by Surov et al. and Drozd et al.

Cocrystallization Techniques

There are different techniques available for preparing pharmaceutical cocrystals, and the

choice of method usually depends on the properties of the drug, coformer, and the solvent being used.

Among these, one of the simplest and most commonly used methods is the solvent evaporation technique. In this approach, the drug and coformer are initially dissolved in a suitable volatile solvent. The solution is then kept undisturbed, usually at room temperature, and allowed to evaporate slowly. As the solvent gradually evaporates, the concentration of both components increases, and this leads to the formation of crystals over time. This method is quite easy to perform and is widely preferred for small-scale laboratory work.[16] Another commonly used approach is the grinding method, which can be carried out either as dry grinding or liquid-assisted grinding. In dry grinding, the drug and coformer are mixed and ground together without using any solvent. In liquid-assisted grinding, a small amount of solvent is added to improve interaction between the components and facilitate cocrystal formation.[17] This method is relatively quick and does not require large amounts of solvent.

Characterization of Cocrystals

After the cocrystals have been prepared, it is very important to determine whether a new crystalline form has actually been formed or not. For checking this various characterization techniques or methods are used. These methods are mainly helpful in understanding the interaction between the drug and the coformer. They also give an idea about any changes occurred in the crystal structure.[18]

a) Fourier Transform Infrared Spectroscopy (FTIR) is most widely used method in evaluation of cocrystals. It is mainly used to study the interaction between the functional groups of the drug and the coformer. If there is any shift in the peaks, it usually indicates the formation of hydrogen bonding or some kind of intermolecular interaction.[19]

b) Differential Scanning Calorimetry (DSC) is also widely used method, which gives information about the thermal behavior which means difference in melting point, when compared to the pure drug, generally suggests that a new crystalline phase may have formed.

c) Scanning Electron Microscopy (SEM) is used to observe the morphology of the cocrystals. The shape and surface of the cocrystals sometimes are different from the pure drug, which again supports their formation. Overall, these techniques are used to evaluating the formation of cocrystals and that give us a better understanding of their properties.[20]

Evaluation of Cocrystals

After preparing cocrystals, it is important to check how they actually perform, not just whether they have formed. For this reason, a few evaluation parameters are usually considered to understand if there is any real improvement in the drug properties. One of the first things that is generally looked at is solubility. Since many drugs have issues with poor aqueous solubility, this step helps in comparing the cocrystal form with the pure drug.[25]

Apart from that, in-vitro dissolution studies are also carried out to understand how quickly the drug dissolves in a given medium. In many cases, cocrystals tend to dissolve faster, although the extent of improvement can vary. Stability is another factor that is usually checked under conditions like temperature or humidity to see how the cocrystal behaves over time.[26] Overall, evaluation gives a clearer idea about whether the prepared cocrystals are useful and suitable for further formulation work.

Similar improvements in solubility and dissolution behavior have been reported in cocrystal systems developed by Naqvi et al.

Applications of Cocrystals

Cocrystals are now being used more often in pharmaceutical research, mainly because they offer a simple way to improve drug properties. One of the main uses is to deal with poor solubility. Many drugs do not dissolve properly in water, and this can affect how well they work. A drug like Luliconazole also faces this issue when combined with a suitable coformer to form

a cocrystal than its solubility can be improved, which is helpful during formulation. Another important application of cocrystals is that they play important role in improvement of dissolution rate. Since cocrystals have a modified crystal structure and better surface properties, they dissolve faster as compared to the pure drug. This can directly help in improving drug absorption and bioavailability.[21]

Cocrystals also help in improving other physicochemical properties such as hygroscopicity, flow properties, and compressibility, which are important during formulation development. Because of these benefits, cocrystal technology are used in modern pharmaceutical research as an effective way to improve drug performance.

Advantages of Cocrystals

Cocrystals are gaining a lot of attention in pharmaceutical industry because they have provided a simple and effective way to improve drug properties.

One of the main advantages is that they increase the solubility of drugs that do not dissolve well in water, such as Luliconazole. When solubility of Luliconazole improves, the drug usually dissolves faster, which can be helpful for better absorption in the body.[22]

Another good thing is that the basic chemical structure of the drug does not change. So, its therapeutic action remains the same, while only the physical properties are adjusted. In some cases, cocrystals may also show better stability compared to amorphous forms, which are known to be less stable.[22]

Limitations of Cocrystals

At the same time, cocrystals are not completely free from challenges. One common issue is selecting the right coformer. Not every combination works, so sometimes it takes a few trials before getting a suitable cocrystal. Another point is scale-up. A method that works fine in the lab does not always translate easily to large-scale production, which can be a bit of a limitation.[23] There can also be some stability-related issues. Such as temperature or humidity that may affects the final product in some cases, so proper storage conditions become important.

Overall, cocrystals are very useful, but they need careful selection of coformers and other expedients also optimization to get consistent and reliable results.

Conclusion

Pharmaceutical cocrystallization is an effective strategy for improving the solubility and dissolution of poorly soluble drugs such as luliconazole. By forming cocrystals with suitable coformers like fumaric acid, the physicochemical properties of the drug can be significantly enhanced without altering its chemical structure. Overall, recent studies strongly support that cocrystallization, along with advanced formulation strategies, significantly enhances the solubility, dissolution, and therapeutic efficacy of luliconazole.

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