IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

Solubility Enhancement of Luliconazole by Solid Dispersion

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Abstract: *Solubility is important parameter for a drug which affects absorption of drug and bioavailability which leads to alter the therapeutic effectiveness. It plays vital role in dissolution process. Most of drugs are practically insoluble in water. Water is the choice of solvent in pharmaceutical industry. The drug should be soluble in GIT for absorption. Therefore, various techniques are used to enhance the solubility of drug. In this study solubility of drug luliconazole in water enhance by using polymer PVP K-30. This technique has shown improvement in solubility of drug. The polymer PVP K-30 is used to improve the solubility of drug. The drug and polymer is used in ratio 1:2 w/w. The best release was 30% in 60 min as compared to pure drug 1% in 60 min.*

Keywords: Luliconazole, PVP K-30, solubility, solid dispersion, UV spectroscopy, FTIR, XRD, DSC

I. INTRODUCTION

Solubility is the property of a chemical compound, referred to as a solute, to dissolve in a solid, liquid, or gaseous solvent and produce a homogenous solution of the solute in the solvent. The solvent is often a liquid, which could be a single substance or a mixture of two liquids. It is rare to discuss a solution that is in a gas, solid solutions are more typical. From being entirely miscible (infinitely soluble), like ethanol in water, to being only marginally soluble, like silver chloride in water, the degree of solubility varies significantly. Chemicals that are just very slightly soluble are commonly referred to as being insoluble.

A saturated solution is one in which the solvent and the solute are in an equilibrium state. Molarity, molality, parts, %, volume fraction, and mole fraction are some of the ways it can be portrayed. It is the quantitative measure of the amount of dissolved solute in a saturated solution at a particular temperature. In terms of quality, it refers to transparent, uniform molecular dispersion, which is the result of two or more compounds continuously interacting to produce one phase.

The simultaneous and antagonistic processes of dissolving and phase joining (such as the precipitation of solids) lead to solubility, which happens when a system is in dynamic equilibrium. In the case of on immediate release agent, solubility is determined by the highest dose strength. When a medication dissolves in 250 ml. or less of aqueous solutions with a pH range of 1 to 7.5, it is said to be very soluble. The estimated volume of 250 ml. comes from normal bioequivalence testing methods, which call for giving a medicinal product to fasting human volunteers with a glass of water. All medications have been separated into four

Categories: class 1, high soluble and high permeable, class II, low soluble and high permeable, class III, low soluble and high permeable, and class IV, low soluble.

In order to complete a movement and achieve the desired pharmacological reaction, solubility in crucial. Drug solubility also serves.

- To improve bioavailability
- Reduce target specificity
- Low bioavailability in animal studies
- Compounds precipitating during serial dilution un buffer, biochemical assays, functional assays, and cell-base assays are some potential complications that could arise from low aqueous solubility.

DOI: 10.48175/IJARSCT-27210

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Table 1: Classification of solubility:

Classification	Parts of the solvent required per part of solute
Very soluble drug	Very soluble drug
Freely soluble drug	From 1-10
Soluble drug	From 10-30
Sparingly soluble drug	From 30-100
Slightly soluble drug	From 100-1000
Very slightly soluble drug	From 1000-100000
Insoluble drug	Greater than 100000

The main issue that arises while formulating new chemical entities as well as developing generics is low water solubility. At the absorption site, all medications that are to be absorbed must be present as an aqueous solution Insoluble in water is a characteristic of more than 40% of NCEs created in the pharmaceutical sector. Thus, one of the biggest difficulties facing formulation chemists is the issue of solubility.

Process of solubilization:

Step 1. In the solubilization process is the breaking of interionic or intermolecular bonds in the solute followed by the separation of solvent molecules to make room for the solute and the interaction of the solvent with the solute molecule or ion. Step 2. A solid molecule separates from the bulk.

Step 3: The solid molecule feed is incorporated into the solvent's hole.

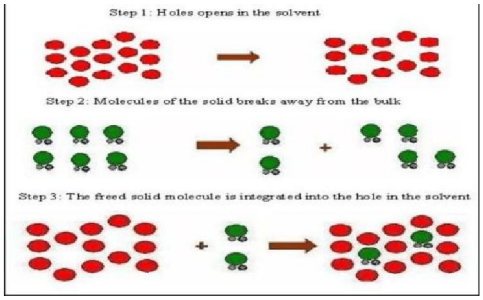

Fig. 1: solubilisation process

Biopharmaceutical classification system (BCS):

The Biopharmaceutics Classification System classifies class II drugs as having a rate preventive step in which the drug is released from the dosage form and solubility in stomach fluid but does not have the absorption, therefore, when its solubility increases, it results in increased bioavailability for class II drugs in the BCS. The BCS drug displays the medicine's permeability and solubility parameters. Both their surface area and their rate of dissolution are larger Consequently, if the area increases with a decrease in particle size, it can be controlled using predictable techniques, such as ball milling, trituration, grinding fluid energy micronization, controlled precipitation, and salt formation. As a result, design strategies for increasing medication bioavailability are being revealed.

Table 2**:** BCS with examples:

Class	Permeability	Solubility	Example
I.	High	High	Propranolol, diazepam, acyclovir, levodopa
II.	High	Low	Nifedipine, naproxen, amlodipine, itraconazole
III.	Low	High	Cimetidine, metformin
IV.	Low	Low	Taxol, colistin, clorthiazol

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Factors affecting solubility:

Particle size. A larger solid particle will be more soluble because, for instance, a smaller element will have a larger surface area and be able to communicate and interact with the solvent more effectively. Solubility is affected by particle size. The surface area to volume ratio rises as article size decreases. Increased particle surface area results in increased solvent interaction.

Temperature. The effect of temperature on solubility. If the energy is absorbed during the solution process, the solubility will rise as the temperature rises. If the energy is released during the solution process, then rising temperature will result in a decrease in solubility.

Pressure: For gaseous solutes, a rise in pressure causes the solubility to increase and a drop causes the solubility to decrease, Changes in pressure have no impact on the solubility of solid or liquid solutes.

The nature of the solute and the solvent is dependent on the solute's concentration in a given amount of solvent at a certain temperature. As an illustration, at room temperature, 200 gram of rime chloride may
dissolve in 100 g of water, whereas only 1g of lead (11) chloride can.

Polarity: The solubility is influenced by the polarity of both the solvent and solute molecules. In general, polar solvents dissolve polar solute molecules and non-polar solvents dissolve non- polar solute molecules.

PH: The majority of medications contain week electrolytes, which cause weak bases and weak acids to ionize the solution. The medications that are more water soluble when they are in ionized form. Unionized drugs have poor water solubility.

Limitations:

- Low loading capacity
- Degradation of drugs
- Expulsion of drugs during storage following polymorphism changes.
- A high water content (70-99.9%)

Techniques To Overcome Poor Solubility:

Chemical modifications:

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropy
- Use of novel solubilizer
- Nanotechnology

Physical modification:

Particle size reduction:
Conventional method
Micronization
Co-grinding and co-micronization
Nano suspension
Precipitation technique
Media milling
High pressure homogenizations
Combined precipitation and homogenization

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Modification of the crystal habit:
Polymorphs
Pseudo polymorphs

Inclusion complex formulation based technique:
Physical mixture
Kneading Method
Co-precipitate

Solubilisation by surfactant:
Micro emulsions
Self-micro emulsifying drug delivery system

Drug dispersion in carrier
Solid solutions
Solid dispersions
Fusion Process

Solvent Method
Fusion solvent method
Spray drying
Lyophilization (Spray Freeze Drying Method)
Hot melt Extrusion
Dropping Method
PH adjustment
Supercritical fluid process
Liquisolid technique
Polymeric alteration
Sonocrystalization
Micellar solubilisation
Crystal engineering
Cryogenic techniques:

Spray freezing onto cryogenic fluids
Spray freezing into cryogenic liquids (SFL)
Spray freezing into vapour over liquid (SFV/L)
Ultra-Rapid freezing (URF)

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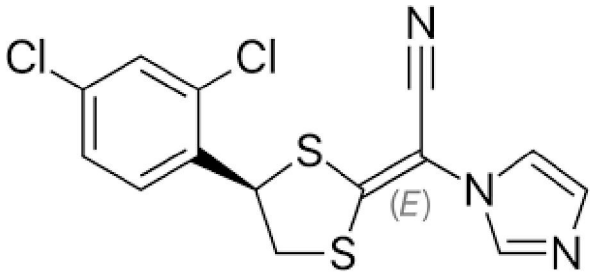
DRUG PROFILE:
DRUG: LULICONAZOLE
Monograph of luliconazole: Structure:



Synonyms:
Lulicon
Luliconazole
NND-502
Luxu

IUPAC Name:
(2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene)-2-imidazol-1- ylacetonitrile
Clinical data:
Formula: C14H9C12N352
Molecular mass: 354.3 g/mol
Melting point: 152 °C
PKA: 634
Half-life: Up to 24 hrs.
Drug category: Antifungal
A uniform dispersion of a small amount of medication in solid form. To provide an optically active R-enantiomer is luliconazole, a topical, broad-spectrum imidazole antifungal medication from the dichlorobenzene class of chemical compounds. The FDA authorized it in November 2013 for the treatment of tinea pedis, corporis, and other fungal diseases brought on by Trichophyton rubrum and Epidermophyton floccosum. Human subjects found it to be safe and well tolerated.
It is poorly soluble in water and highly permeable. It is less toxic and well tolerated it has both fungistatic and fungicidal actions. The epidermis, dermis, and deeper layers of skin are all affected by fungus infections, so it's important to tailor medication administration so that high drug concentrations are localized at the epidermis and dermis layers
In the current study. LZL nanocrystals were added to a hydroalcoholic gel to increase medication absorption and skin retention at the site of infection

Mechanism of action:
A member of the azole class of medications, Luliconazole is an antifungal. Luliconazole appears to prevent ergosterol formation by obstructing the enzyme lanosterol demethylase, while the precise mechanism of action against dermatophytes is uncertain. A drop in the amount of ergosterol, a component of fungal cell membranes, and a corresponding buildup of lanosterol occur when this enzyme's activity is inhibited by azoles.

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Pharmacokinetics:

Absorption:

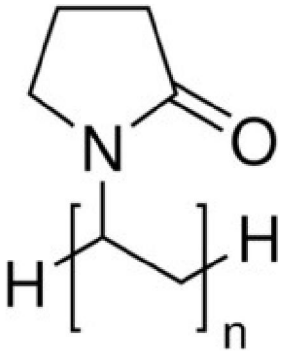
Despite the fact that luliconazole is applied topically, clinical investigations have shown that after the initial dose, it reached its maximal plasma concentration in patients with tina pedis in 16.9.9.39 hours tina SD), at 0.40 0.76 ng/ml. (man SD

Distribution: No quantification of Distribution was made.

Metabolism: Metabolism of Luliconazole has yet to be determined.

Elimination: Elimination of luliconazole has yet to be determined.

Polymer: Pollyvinylpyrolidone (PVP K 30)



Synonym:

Povidone
PVP
Kollidon
Poly(1-vinyl-2-pyrrolidinone)
1-ethylene-2-pyrolidinone homopolymer
Specification:
Formula: (C6H9NO)n
Average Molecular weight: 40000
Molar mass: 111.143
Density: 1.69gm /cm³
Melting point: 130°c
Boiling point: 90 - 93 °c
Water solubility: >= 10g / 100 * ml at 20°c
Appearance: white powder
Storage condition: Room temperature
Use: used as stationary phase for gas chromatography

Mechanism of action:

The mechanism includes free radical polymerization of N-vinylpyrrolidone in water (aqueous solution) making use of hydrogen peroxide as initiator. By terminating the polymerization at any stage by regulating the concentration of hydrogen peroxide, the process can produce different molecular weights of soluble PVP.

Solubility enhancement:

a) Organoleptic properties of drug
a) Micromeritics study.
Preformulation stady

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Organoleptic properties:

Drugs was tested for organoleptic properties such as appearance, colour, odour, taste, etc.

Micromeritics study:

Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined It is the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal.

Angle of repose $\theta = \tan^{-1}(\mu)$ Where, h=height=radius **Procedure:**

20gms of the sample was taken the sample was passed through the funnel slowly to form a heap. The height of the powder heap formed was measured. The circumference formed was drawn. With a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density= M/V

Where, M= mass of the powder Vo=bulk volume of the powder

Tapped density:

A graduated cylinder was filled with a specified amount of powder, and the volume Vo was recorded. A density measurement device's attached cylinder wan tapped 500 times before the trading was taken. By mechanically tapping a measuring cylinder containing the powder sample, the density is obtained. The cylinder in mechanically tapped out the minimal volume is detected and volume readings are taken until minimal additional volume change is seen

Tap density-MV

Where, M-man of the powder, V final tapping volume of the powder

Compressibility index and Hausner ratio:

While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume, (VO), and the final tapped volume, (Vo), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows

Compressibility index-100x Vo-Vf/Vo Hausner ratio Vo/VI

Where, Vo= apparent volume, Vf= final tapped volume

Alternatively, the compressibility index and Hausner ratio may be calculated using measured

Values of bulk density and tapped density as follows: Compressibility index=100 x tapped density/bulk density Hausner ratio= tapped density/bulk density

Table No. 3: Flow properties:

Sr.no.	Flow properties	Angle of repose	Compressibility index	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-67	1.46-1.59
7	Very-very poor	>66	<38	>1.6

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Powder X-ray diffraction (XRD) studies:

The powder X-ray diffraction analysis was conducted for pure and treated drug, polymers, physical mixtures and solid dispersions. X-ray diffractograms were obtained using the Siemens (Germany) X-ray diffractometer with Cu-Kα (λ= 1.54 A) radiation at 40 kV and 30 mA. All the samples were scanned and data was collected.

Differential scanning calorimetry (DSC):

Accurately weighed samples (Pure drug and PVP K 30) were placed into the standard aluminium pans with lids. Subsequently, the physical status of PRX of the formulations was monitored using the differential scanning calorimetry (DSC60, Shimadzu, Japan). The heating rate was 20" C/ min and the heat flow was recorded from 25° C to 250 °C. The aluminium oxide was used as reference.

Fourier transform infrared (FT-IR):

Spectroscopic analysis FTIR spectra of the treated and pure powder of luliconazole and solid dispersions were obtained using a Spectrum 65 FT-IR Spectrometer (PERKIN ELIMER) by potassium bromide (KBR, 150 bar) pellet method. The scanning range was 450-4000 cm-1.

First only KBr pellet was made and scanned then the pellet of drug and and KBr was made in ratio of 1:100 and scanned 296nm scanning range was 450 - 4000cm -1.

Results and discussion:

Preformulation result of drug luliconazole

Physical characters:

Sr.no.	Characters	Inference
1	Nature	Powder
2	Colour	White
3	Odour	Characteristics
4	Melting point	150-152 °C

Micromeritics properties:

Sr.no.	Parameters	Inference
1	Bulk density	0.33
2	Tapped density	0.46
3	Angle of repose	40.02
4	Carrs index	21.12
5	Hausners ratio	1.28

Preformulation study:

FTIR:

Sr.no.	Frequency	Functional group
1	3415.7	-OH and-NH stretching
2	1512.1	Aromatic-C-C=H
3	3440.8	-OH stretching
4	1554.63	Aromatic-C=C-
5	1641.4	C=O stretching

Calibration curve:

From the calibration curve of drug slope was determined Le. mm 0.0609. Which used to calculate solubility of drug in water.

Drug content:

The drug content was found to be 0.0038mg.

Saturation solubility:

Solubility of drug in water was found to be 0.004mg/ml

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Saturation solubility of mixture:

Solubility of physical mixture of drug and PVP K 30 was found to be 0.007mg/ml

Dissolution:

Approximately dissolution was observed to be increased. Dissolution was improved due to hydrophobic interaction between drug and water.

Dissolution was found to be 34.166%

II. CONCLUSION

Luliconazole is a topical antifungal drug with lower bioavailability problem due to its poor aqueous solubility, improving the solubility could increase the dermal bioavailability and thus polymer PVP K 30 was added to enhance the solubility of drug in aqueous medium.

Evaluations were done to observe the solubility of drug after addition of PVP K 30. It was observed and therefore concluded that the solubility of drug increase by adding polymer by saturation solubility study of drug and physical mixture.

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