PREFORMULATION STUDUIES ON A DRUG: MICONAZOLE

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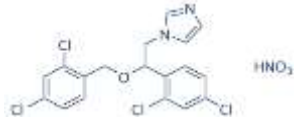
ABSTRACT:- Miconazole nitrate is an anti- fungal drug which belongs to category Azoles (specifically imidazole) drug with a poor aqueous solubility, which requires the development of new delivery system to improve therapeutic activity. Fungal infections are caused by the microscopic organisms that invade the epithelial tissue. Miconazole nitrate bind to the heme moiety of the fungal cytochrome P-450 dependent enzyme lanosterol 14-α-demethlyase. Inhibits enzyme 14-α-demethlyase, blocks the synthesis of ergosterol and leads to the build up of toxic methylated 14-α-sterols. Both effects serve to inhibit cell growth. Miconazole is a lipophillic drug so its permeability is easy for the permeation of drug with the help of permeation enhancer. Some preformulation studies of drug were carried out during the process such as solubility, calibration curve using UV-Visible spectrophotometer, maximum wavelength, Melting point by capillary method, partition coefficient. It concluded that all the preformulation studies were found as per limits.

Keywords: Miconazole nitrate, preformulation studies, UV- visible spectrophotometer.

INTRODUCTION

Miconazole nitrate is an antifungal medication used to treat ring worm, and yeast infections of the skin or vagina. Sold under the brand name **Monistat** and is used for ring worm of the body, groin (jock itch), and feet (athlete's foot). It is used to put over the skin or vagina as a cream or ointment. The molecular weight of miconazole is 416.14, and its chemical formula is l-{2-(2,4-dichlorophenyl)-2 [(2,4-dichlorophenyl) methoxy ethyl]-1H-imidazole.It is also used for the treatment of coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, and chronic mucocutaneous candidiasis.



There are some common side effects which may be generated include itchiness or irritation of the area in which it was applied. Use in pregnancy is believed to be safe for the baby. Miconazole is in the imidazole family of medications. It works by decreasing the ability of fungi to make ergosterol, an important part of its cell membrane.

Pharmacodynamics

Miconazole inhibits the enzyme 14α-sterol demethylase, which decreases production of ergosterol. In addition related to their antifungal actions, miconazole, similarly ketoconazole, is known to act as an antagonist of the glucocorticoid receptor.

Pharmacokinetics

Absorption by route of exposure

Orally, miconozole is incompletely absorbed from the gastrointestinal tract; peak plasma concentrations of about 1 mcg/mL have been achieved 4 hours after a dose of 1 g.

Parenterally, doses above 9 mg/kg body-weight usually produce plasma concentrations above l mcg per mL.

Topically, little absorption through skin or mucous membrane when miconazole nitrate is applied topically.

Distribution by route of exposure

Miconazole is bound to plasma proteins over 90%. The volume of distribution for *miconazole is approximately 1400 L; the drug is 91-93 percent bound to protein, largely albumin.

Metabolism

Miconazole is metabolised in the liver in the form inactive metabolites. Hepatic metabolism of miconazole is generally occurred by O-de alkylation and oxidative N-de alkylation.

Elimination by route of exposure

Orally, approx 50% of an oral dose may be excreted mainly unchanged in the faeces. From 10 - 20% of an oral dose is excreted by urine, as metabolites, within a week .

Parenterally, 10 to 20% of an intravenous dose is excreted in the urine, mainly as metabolites, within 6 days; After an intravenous dose of Miconozole, 40% of the radioactivity is found in faeces and 18% in urine. About 14 to 22% of the dose is excreted via the kidneys, mainly in the form of inactive metabolites.[1-3]

Fungal infections are the fungus that invades the tissues can cause a disease that confined to the skin spreads into the tissues, bone and organs or affects the whole body. Its symptoms are included such as darkening of skin, loss of colour, peeling, rashes, or small bump. Fungal infection of skin is now-a-days one of the most common dermatological problems. Infection is caused by microscopic organisms that invade the epithelial tissue. The fungi kingdom includes yeasts, moulds, and mushrooms which are commonly found on the skin, throat, rectum and vagina. The incidences of mycoses especially superficial fungal infections are increasing and cover more than 25% of the world's population. It is found that disease progression is very rapid, and severity increases in patients with compromise immune function.[3-4]

MATERIAL AND METHODS

Miconazole was obtained from the Akums private limited company which is located in haridwar, dehradun, uttarakhand.

PREFORMULATION PARAMETERS [5-8,14]

Preformulation studies are defined as the investigation of physicochemical properties of the drug. It is a phase which is initiated once the new molecule is seeded. In a broader way, it accord with studies of physical, chemical, analytical and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance.

Objective of the preformulation study is to develop and design the stable, effective and safe dosage form by obtaining kinetic rate profile, compatibility with the other ingredients and establish physicochemical parameters of new drug substances.

Physicochemical parameters are:

1. Organoleptic properties:
   - 1.1. Color
   - 1.2. Odor
   - 1.3. State/form
   - 1.4. Melting point
   - 1.5. Bulk characterisation studies
     - 1.5.1.1. Crystallinity and polymorphism
     - 1.5.1.2. Hygroscopicity
     - 1.5.1.3. Fine particle characterisation
     - 1.5.1.4. Bulk density
     - 1.5.1.5. Tapped density
     - 1.5.1.6. Powder flow properties
       - 1.5.1.6.1.1. Angle of repose
       - 1.5.1.6.1.2. Hausner's ratio
       - 1.5.1.6.1.3. Carr's Index

2. Solubility analysis:
   - 2.1. Intrinsic solubility determination
   - 2.2. Dissociation (pKa) constant
   - 2.3. Partition coefficient
   - 2.4. Dissolution studies
3. Maximum wavelength of drug
4. Standard curve or calibration curve of drug
5. Stability analysis:
   - 5.1. In toxicology formulations
   - 5.2. Solution stability
   - 5.3. Solid state stability

1. Organoleptic properties

1.1. **Colour**: It should be unappealing to the eye and determined by instrumental and visible methods that varies from batch to batch.

1.2. **Odor and taste**: For unpalatable drugs use of less soluble chemical form or suppress it by flavours, excipients, coating etc. Drug substances which produce irritation to skin should be handle with precautions. Flavours, dyes etc used will affect the stability and bioavailability. odor may be pungent, sulphurous, fruity, aromatic and odourless.

1.3. **Bulk characterisation studies**: It is required to identify all the solid form that may exist a consequence of the synthetic stage such as the presence of polymorphs.

1.3.1.1. **Crystallinity and polymorphism** [8-9]: The structure of solid compound called as crystallinity & these structure disappear in the liquid and vapour states. It can be classified as internal structures (cubic, tetragonal, hexagonal, rhombic, etc.), solid habits (platy, needle, prismatic, bladed etc.) Polymorphs is defined as the characteristics of being able to assign a different meaning to something in different context specifically , to allow an entity such as a variable or an object having more than one form.

1.3.1.2. **Hygroscopicity**[9-12]: Many drugs have tendency to absorb moisture. These are classified as: A) Deliquescent [substance which absorb moisture form atmosphere to dissolve itself at higher extreme]. B) Efflorescent [substance which looses water to form a low hydrate or become anhydrous]. C) Hygroscopic [substance that exist in a dynamic equilibrium with water]. Hygroscopicity Classification

Class 1 Non- Hygroscopic- no moisture increases occur at relative humidities below 90%.
Class 2 Slightly hygroscopic- no moisture in occur at relative humidity below 80%
Class 3 Moderately hygroscopic- on storage (one week) Moisture Content does not increase more than 5% at relative humidity below 60%
Class 4 Very hygroscopic- Moisture content increase may occur at relative humidity as low as 40 to 50

1.3.1.3. **Fine particle characterisation**: it is necessary to develop as early as possible how the particle size of the drug substance may affect formulation and product efficacy. Particke size distribution may affe t the drug dissolution rate, bioavailability and stability.

1.3.1.4. **Bulk density** [8-12]: It is defined as the dry weight of substances per unit volme of substances. pb= M/V , where pb is bulk density, M is weight of powder and V is volume of powder.

1.3.1.5. **Tapped density**: It is defined as obtained by mechanically tapping the measuring cylinder containing powder.

1.3.1.6. **Powder flow properties**: During the process of preformulation evaluation of the drug substance, therefore, its flow ability characteristics should be studied, especially when the expect dose is large. Powders may be free flowing or cohesive that may affect by changing in particle size, density, shape etc.

1.3.1.6.1.1. **Angle of repose**: The maximum angle formed between the surface of pile of powder and horizontal surface or base line is called the angle of repose.

$\tan \theta = h / r$

h = height of heap of pile, r = radius of base of pile

Flow Character	Angle of repose
Very good	<20
Good	20-30
Poor	30-34
Very poor	>40

Table No.1

1.3.1.6.1.2. **Hausner's ratio**: It is defined as the ratio between the tapped bulk density and oxygenate or freshen bulk density.

Hausner's ratio	Hausner's ratio
1.00-1.11	Excellent/very free flow
1.12-1.18	Good/free flow
1.19-1.25	Fair
1.26-1.34	Passable

1.5-1.45	Poor/cohesive
1.46-1.59	Very poor/very cohesive
>1.60	Very, Very poor/approx. Non-flow

Table No.2

1.3.1.6.1.3. **Carr's index**: Also called as compressibility of powder. Defined as the ability of a powder to decrease in volume under pressure.

Carr's index (%)	Type of flow
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, Very poor

Table No.3

2. **Solubility analysis**: One important goal of the preformulation effort is to devise a method for making solutions of the drug. A drug must have some aqueous solubility for therapeutic efficacy.

2.1. **Intrinsic solubility determination**: Amount of drug is dissolved in a medium and mix it at constant temperature, withdraw the samples at interval time, clarify with filtration process and assayed it using UV, HPLC&GC.

Table No.4

Descriptive solubilities (I.P.)

Descriptive forms (solubility definition)	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Insoluble or practically insoluble	More than 10,000

2.2. **Dissociation (pKa) constant**: The interrelationship of the dissociation constant, lipid solubility and pH at the absorption characteristics of various drugs are the basis of the pH-partition theory.

2.3. **Partition coefficient**[8-11]: The oil/water partition coefficient is defined as a measure of a molecules lipophillic characters that is, its preference for the hydrophilic or lipophillic phase. The Henderson -Hasselbach equation provides an quantity of the ionized and unionized drug concentration at a particular pH. For acidic compounds, pH = pKa + log (un-ionized drug) / [ionized drug] for basic compounds, pH = pKa + log (ionized drug) / [un-ionized drug].

2.4. **Dissolution studies:** The speed or rate at which drug substance dissolves in a medium is called dissolution rate.

3. **Maximum wavelength of drug**: It refers to the wavelength in the absorption spectrum where the absorbance is maximum. Generally also called as lambda max. Symbol denoted as λ.

4. **Standard curve or calibration curve of drug:** It is a type of graph used as a quantitative research technique. Many samples with well known properties are measured and graphed, which then permits the same properties to be determined for unknown samples by interpolation on graph.

5. **Stability analysis**:

5.1. **In toxicology formulations:** These studies are recommended to assess samples of toxicology preparations for stability and potential homogeneity problems. Using animals we can find the toxicity in formulations.
5.2. **Solution stability**: These studies include the effect of pH, ionic strength, co-solvent, light, temperature and oxygen.
5.3. **Solid state stability**: The main objective of those study is investigation and identification of stable storage condition for drug in the solid state and identification of compatible excipients for a formulation.

RESULTS AND DISCUSSION

1. **Organoleptic properties**:

1.1. **Colour:** White to pale cream.

Fig. No. 1: Pure form of miconazole nitrate (drug)

1.2. **Odour**: Odourless or almost odourless.
1.3. **State/form**: Crystalline or microcrystalline powder.
1.4. **Melting point**: 130˚C.
1.5. Bulk characterisation studies:

1.5.1.1. **Bulk density**: We found the bulk density of drug was o.332.
1.5.1.2. **Tapped density**: We found the tapped density of drug was 0.395.

1.5.1.3. Powder flow properties:

1.5.1.3.1.1. **Angle of repose**: We found the angle of repase of drug was 0.66, it means that it possessed excellent flow.
1.5.1.3.1.2. **Hausner's ratio**: We found the hausner's ratio of drug was 1.189, it means that it has a good or free flow property.
1.5.1.3.1.3. **Carr's Index**: We found that the carr's index of drug was 15.94, it means that it possessed excellent flow properties.

2. Solubility analysis:

2.1. **Partition coefficient**: The partition coefficient of Miconazole nitrate in n-octanol and water was obtained 17.72.

2.2. **Intrinsic solubility determination:**

S.NO.	DESCRIPTIVE FORMS (SOLUBILITY DEFINITION)	PARTS OF SOLVENT REQUIRES FOR ONE PART OF SOLUTE	SOLVENT
1.	Freely soluble	From 1 to 10	Ethanol & methanol
2.	Sparingly soluble	From 30 to 100	Chloroform
2.	Slightly soluble	From 100 to 1,000	Acetone
4.	Insoluble	>10,000	Water

Table No.5

3. **Maximum wavelength of drug**: We found maximum wavelength of drug by using UV-Visible spectrophotometer was 246 nm.

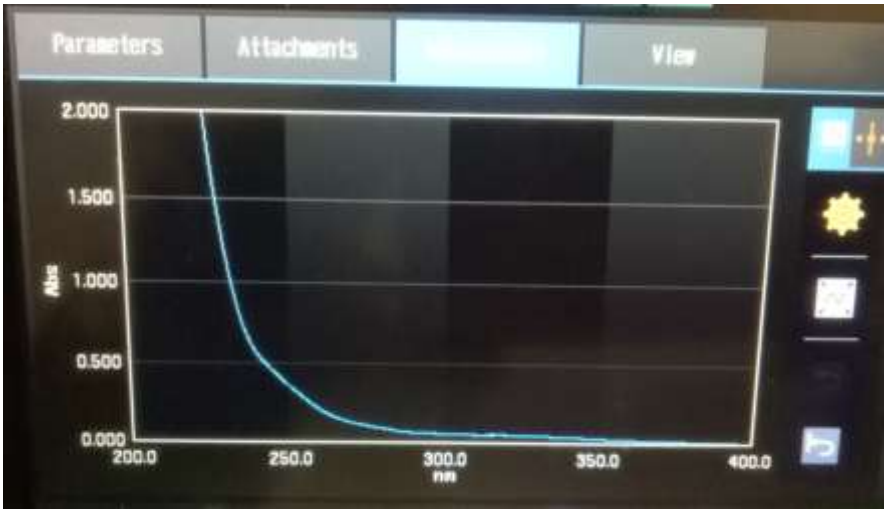


Fig. No.2: Spectrum of Miconazole Nitrate

4. **Standard curve or calibration curve of drug**:

4.1. Calibration curve for miconazole nitrate in **ethanol**

S.NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	5	0.341
3	10	0.466
4	15	0.557
5	20	0.609
6	25	0.729
7	30	0.864

Table No.6

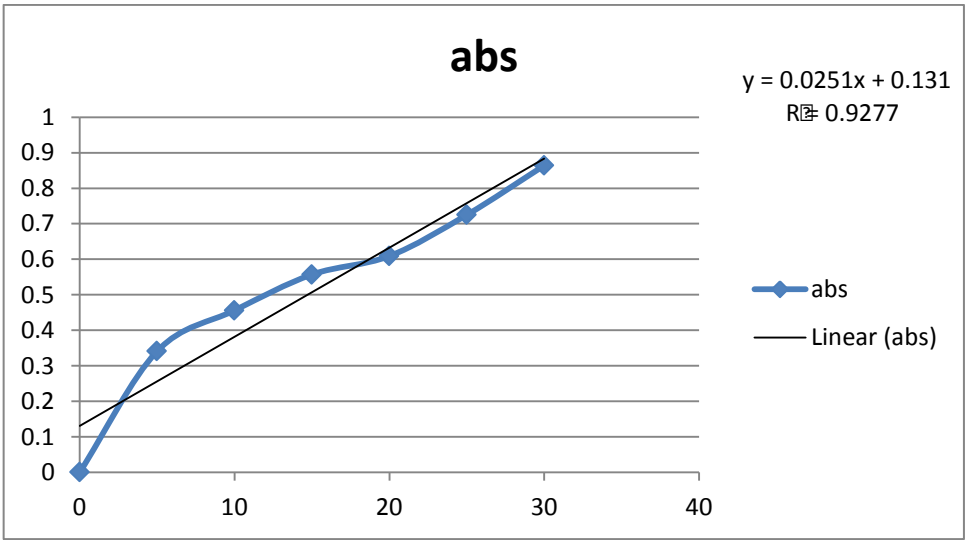


Fig. No. 3: Calibration curve of drug in ethanol

4.2 Calibration curve for miconazole nitrate in **6.8 phosphate buffer**

S.NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	5	0.193
3	10	0.295
4	15	0.318
5	20	0.427
6	25	0.532
7	30	0.631

Table No.7

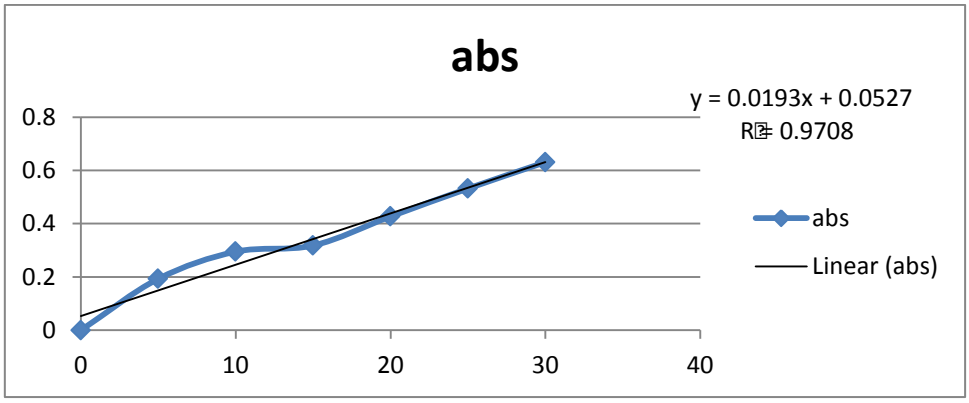


Fig. No. 4: Calibration curve of drug in 6.8 phosphate buffer

4.3 Calibration curve for miconazole nitrate in **7.4 phosphate buffer**

S.NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	5	0.204
3	10	0.391
4	15	0.441
5	20	0.492
6	25	0.521
7	30	0.693

Table No.8

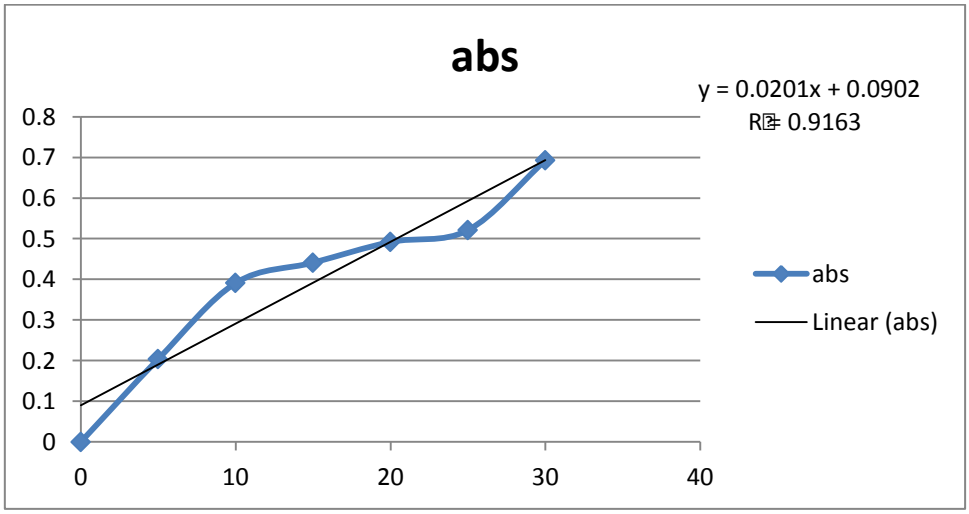


Fig. No. 5: Calibration curve of drug in 7.4 phosphate buffer

CONCLUSION

Preformulation studies have a important part to play in expecting formulation problems and identifying relevant paths in both liquid and solid dosage form Technology. By comparing the physicochemical properties of each drug candidate within a therapeutic group, the Preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization. In parallel solid-state stability by DSC, TLC and HPLC in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage form. As we knew the miconazole nitrate possess broad spectrum of antifungal activity and all the physicochemical parameters limit range of the drug came under the standard limits.

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