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A REVIEW ON COMPARATIVE STUDY OF DIFFERENT BRANDS OF KETOCONAZOLE DRUG

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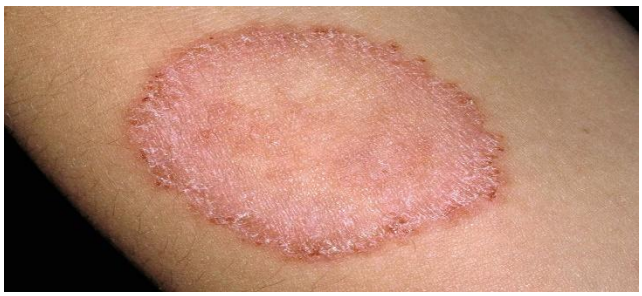
ABSTRACT:

Ketoconazole is a drug used in the management and treatment of fungal infections. It is in the imidazole antifungal class of medications. This activity describes the indications, actions, and contraindications of ketoconazole as a valuable agent in treating fungal infections. This activity will highlight the mechanism of action, adverse event profile, and other key factors pertinent to members of the inter professional team in the treatment of patients with fungal infection. The in vitro study was done by performing various test procedures associated to assess the quality of tablets. The brands had been passed for the weight variation tests, because no tablets cross the ± 10 % weight variation. According to the test procedure by using Monsanto hardness tester brands of Ketoconazole tablets were within the specified limit. Percentage friability of the four brands was not more than 1% and thus they met the specifications. The entire brand disintegrated more than 85% within 20 minutes and thus they complied with the specifications. In conclusion, in the quality control parameters studies, all brands of Ketoconazole tablet had shown satisfactory results.

Keywords Ketoconazole, quality, weight variation, hardness, friability, disintegration, dissolution

Introduction :

Ketoconazole IUPAC name 1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3- dioxolan4yl] methoxy] phenyl] piperazin-1-yl] ethenone is mainly used as an antifungal antibiotic and also used to prevent yeast infections in patients who are likely to become infected, because they are being treated with chemotherapy or radiation therapy before a bone marrow transplant



Skin fungus

A fungus is a tiny organism, such as Mold or mildew. Fungi are everywhere — in the air and water and on the human body. About half of fungi are harmful. If one of the harmful fungi lands on your skin, it can cause a fungal infection

You may have a higher risk for developing a skin rash.

- Have a weakened immune system (for example, if you take immunosuppressant medications, have a disease that weakens the immune system or are undergoing chemotherapy
- Take long-term or high-dose antibiotics.
- Have excess weight.
- Have diabetes.

Types of fungal infections include the medical name for a fungal skin infection is tinea. Types of fungal infections include:

1. Athlete's foot (tinea pedis): The most common type of fungal infection, this condition often spreads when people walk barefoot in public bathrooms or locker rooms. The skin between your toes turns white and starts to peel. Athlete's foot can also affect the soles (bottoms) of the feet.

2. Nail fungus (onychomycosis): This infection is a common foot problem. It usually affects the toenails, which become yellow and thick and break easily.
3. Jock itch (tinea cruris): A rash of the groin area, jock itch affects more men than women. Scalp ringworm . This rash occurs mostly in children. It causes hair loss, but with the right treatment, the hair usually grows back.

Causes a fungal rash

When your skin comes into contact with a harmful fungus, the infection can cause the rash to appear. For example, if you borrowed a pair of shoes from someone who had athlete's foot, the fungus could come in contact with your foot and infect you. Rashes often pass from person to person or from animal to person by direct contact.

Symptoms of a fungal rash -

- A fungal rash is often red and itches or burns.
- You may have red, swollen bumps like pimples or scaly. Flaky patches

Fungal rash diagnosed-

A healthcare provider may be able to diagnose a fungal rash by looking at it and asking about your symptoms. Many times, the diagnosis can be confirmed by examining scrapings of the scale under the microscope (KOH preparation). In some cases, you may need a fungal culture test to identify a specific fungus and help determine the best treatment for you. During a fungal culture test, your provider may take a small sample of skin (biopsy) or fluid (aspiration). For severe infections, you may need a blood test.

Treatment for skin fungus includes

Antifungal creams, many of which are available over-the-counter. Stronger prescription medications, which may work faster. Oral medicines, if the fungal infection is severe. Ketoconazole, sold under the brand name Nizoral among others, is an antiandrogen and antifungal medication used to treat a number of fungal infections. Applied to the skin it is used for fungal skin infections such as tinea, cutaneous candidiasis, pityriasis versicolor, dandruff, and seborrheic dermatitis. Taken by mouth it is a less preferred option and only recommended for severe infections when other agents cannot be used
Ketoconazole was patented in 1977 by Belgian pharmaceutical company Janssen, and came into medical use in 1981. It is available as a generic medication and formulations that are applied to the skin are over the counter
In the United Kingdom. In 2020, it was the 170th most commonly prescribed medication in the United States, with more than 3 million prescriptions. The formulation that is taken by mouth was withdrawn in the European Union and in Australia in 2013, and in China in 2015 In addition, its use was restricted in the United States and Canada in 2013 Ketoconazole was patented in 1977 by Belgian pharmaceutical company Janssen, and came into medical use in 1981. It is available as a generic medication and formulations that are applied to the skin are over the counter in the United Kingdom. In 2020, it was the 170th most commonly prescribed medication in the United States, with more than 3 million prescriptions. The formulation that is taken by mouth was withdrawn in the European Union and in Australia in 2013, and in China in 2015 In addition, its use was restricted in the United States and Canada in 2013.
The quality of pharmaceuticals is a global concern; counterfeit medicines are increasingly detected worldwide. Quality of pharmaceutical product is the most essential for efficacy and safety of product. Quality of product defines to its confining to the standards pre-set to assure the desired purpose. Pre requirement of drug products that should be chemically and pharmaceutically equivalent, must be identical in strength, quality, purity, active ingredient release profile and also in the same dosage form, for the same route of administration. In order to ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product. It is needed to ensure that the generic and branded drugs products are pharmaceutically equivalent moreover, it also necessity to choose one product from several generic drug products of the same active ingredients. Generic drugs share large portion of the marketed medicines in treating diseases.
Generic drugs have entered the market soon after the patent granted to the manufacturer of an originator‖ drug has expired. Generic drugs are a major asset to national projects as they are the economic alternative of the costlier brand name drugs and create true market competition. Consequently, the use of generic drugs has rapidly increased and now dominates the medication landscape for patient use. Patients and health professionals assume that generic drugs compete with brand drugs, and are manufactured and marketed by companies that compete with brand drugs. The quality control and assurance of pharmaceuticals depend on monitoring some parameters like the composition and uniformity of the drug during processing as well as in the final product. Some bioavailability studies indicated that similar therapeutic responses were not exhibited from tablets with same drug and drug content. The variation of performance properties of tablets and therapeutic effects are due to some factors like excipients used in the manufacturing of tablets, physical characteristics of the drug and the manufacturing process. Drug quality is becoming a concern in developing countries. Because of the poor monitoring activities of drug regulatory bodies in these countries, there is high chance of circulation of lower quality drugs in the market which may affect the health and trust of public

Objectives

The main objective to undertake this study is to show a comparison between different brands of same drug available in India on the basis of various evaluation tests including study of quality parameters such as weight variation test, hardness test, friability test, disintegration test, dissolution test

studies among the different brands of Ketoconazole tablet. To know the efficacy of different brands of different pharmaceutical industry

Drug Profile

- Drug Name: - Ketoconazole
- IUPAC Name: - 1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4- eel] methoxy] phenyl] piperazin-1-yl] ethenone
- Colour / Form: - White crystalline powder
- Molecular Formula: - C26H28Cl2N4O4
- Synonyms: - Funicle, Ketoconazole
- Molecular Weight: - 5 3 1. 4 1 g / M o l
- **Category:** - Antifungal Antibiotic Drug Belongs To imidazole Class. Dose: - Tablet Ketoconazole 200 mg

- **Solubility:** - (17 µg/ml) Ketoconazole has very low solubility in the water and higher penetrability; therefore, it has been considered as a class II drug in the bio pharmaceutics classification system (BCS)
- **Melting Point:**- 147 °C (297 °F)
- **Boiling Point**:- 753.4±60.0 °C
- **Standard Storage condition**: - Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep from freezing.

Pharmacokinetics

Ketoconazole is an orally effective, broad-spectrum, systemic antifungal agent. The pharmacokinetics and bioavailability of ketoconazole given as a 200-mg single dose in a tablet, suspension, or solution were studied in 24 fasting healthy males by using a crossover design. Levels of ketoconazole in plasma were determined for up to 48 h by a sensitive reverse-phase high-performance liquid chromatography method. The absorption of ketoconazole was rapid, with mean maximum concentrations of the drug in plasma of 4.2, 5.0, and 6.2 micrograms/ml attained at 1.7, 1.2, and 1.0 h, respectively, after administration of the tablet, suspension, and solution, respectively. The mean distribution and elimination half-life values were 1.5 to 1.7 and 7.5 to 7.9 h, respectively. The mean oral clearance of the solution dose was 209 (+/- 82.9 [standard deviation]) ml/min, and the mean apparent volume of distribution was 88.31 (+/- 68.72) liters. The relative bio availabilities for the tablet and suspension were 81.2 (+/- 33.5) and 89.0 (+/- 23.1) %, respectively, of that of the solution. The data indicated the bioequivalence of the tablet to the suspension and of the suspension of the solution. Dose proportionality of ketoconazole was also studied in 12 volunteers after they received solution doses of 200, 400, and 800 mg. Linear correlations between the dose and maximum concentration of the drug in plasma

Route of Elimination

In normal volunteers, Ketoconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose measured in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites. A study of a 50mg radiolabelled dose of Ketoconazole revealed that 93.3% of the dose was found excreted in the urine. A note on renal failure. The pharmacokinetics of Ketoconazole are significantly affected by renal dysfunction. The dose of Ketoconazole may need to be reduced in patients with decreased renal function. A 3-hour haemodialysis treatment lowers plasma Ketoconazole concern

Study Design:

Comparative in vitro quality control parameters between the commercially available tablet brands of ketoconazole in India were studied through the evaluation of weight variation, hardness, friability, disintegration time, dissolution time. The study was done by performing various test procedures associated to assess the quality of the tablets

Sr. no	Brand Name	Batch No	Mfg. Date	Exp. Date	MRP	Mfg. Lic. No	Mfg. By
1	Amiketo 200	KT21I01	NOV. 22	OCT. 24	152	NKD - 56	Amigoz

2	Ketowell 200	N410374	DEC. 22	NOV. 24	119	27/UA/LL/2006	Wellona Pharma
3	DR. Zip	072A043	JAN. 23	DEC. 25	160	656	Dr. Best

Table no.1: Label information about sample

Sr. no	Brand Name	Colour	Shape
1	Amiketo 200	White	Rectangle
2	Ketowell 200	White	Round
3	Dr. Zip	White	Round

Table no. 2: Physical appearance of different brand

Volume of Distribution

Ketoconazole has an estimated volume of distribution of 25.41 L or 0.36 L/kg. It distributes widely among the tissues, reaching effective concentrations in the skin, tendons, tears, and saliva. Distribution to vaginal tissue produces concentrations 2.4 times lower than plasma.

Clearance

Ketoconazole has an estimated clearance of 8.66 L/h

Metabolism

Absorption from the gastrointestinal tract, NIZORAL is converted into several inactive metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of ketoconazole. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, by hepatic microsomal enzymes. In addition, oxidative O-dealkylation and aromatic hydroxylation does occur. Ketoconazole has not been demonstrated to induce its own metabolism.

Biological Half-Life

Ketoconazole has not been demonstrated to induce its own metabolism. Elimination from plasma is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Approximately 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged

Pharmacodynamics

Ketoconazole, similarly to other azole antifungals, is a fungi static agent which causes growth arrest in fungal cells thereby preventing growth and spread of the fungus throughout the body. As an antifungal, ketoconazole is structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a College of Pharmacy, Medha 12 constituent of fungal cell membranes, as well as certain enzymes. As with all azole antifungal agents, ketoconazole works principally by inhibiting the enzyme cytochrome P450 14αdemethylase (CYP51A1). This enzyme participates in the sterol biosynthesis pathway that leads from lanosterol to ergosterol. Lower doses of fluconazole and itraconazole are required to kill fungi compared to ketoconazole, as they have been found to have a greater affinity for fungal cell membranes.

Mechanism of Action

Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane

Side effects

- Chest pain
- Hives
- Difficulty breathing
- Swelling in your face or throat
- Fever,
- Sore throat
- Burning eyes
- Skin pain

Methodology

1. Weight Variation Test

Twenty tablets from each brand of Ketoconazole were weighted individually with the mentioned analytical balance and average weight and the percent deviation was determined for each brand. The

equation for calculation of percentage weight variation is given below: Percentage weight variation= (average weight - individual weight) individual weight x 100%. Sr. No Brands Average w.(g) Weight variation

Sr.no	Brands	Average w.(g)	Weight variation limit
1	Amiketo 200	0.318	-7.5 to +7.5%
2	Ketowell 200	0.305	-7.5 to +7.5%
3	Dr. Zip 200	0.311	-7.5 to +7.5%

Table no. 3: The weight variation limit of different brands

2. Hardness Test

Tablet hardness is typically expressed as the load necessary to crushing a tablet placed on its edge and hardness is sometimes termed the tablet crushing strength. The suitability of the tablet in considers to mechanical stability during packaging and shipment can usually be predicted on the basis of hardness. The crushing strength was determined with a tablet hardness tester (Monsanto). Four tablets were randomly selected from each brand for this

Sr.no	Brands	Average hardness (kg/f)
1	Amiketo 200	6.61
2	Ketowell 200	6.75
3	Dr.Zip 200	6.52

Table no.4: Average Hardness of different brands

3. Friability Test

The experiment was started by weighing 10 tablets altogether which is considered as the initial weight, W1. All the tablets placed in the drum of friability tester and the equipment was rotated 100 rpm for 4 min (i.e. = 25 rpm for 1 min). Then the tablets were taken out, deducted, and reweighed (only the intact ones). This is considered as the final weight, W2. Then the percentage loss of weight of the tablets was calculated by using following equation10. Percentage friability= {(Initial weight- Final weight)/ Initial weight} x100

Sr.no	Brands	Average % of friability
1	Amiketo 200	0.25
2	Ketowell 200	0.22
3	Dr.Zip 200	0.20

Table no.5: Average % of friability of different

Disintegration Test

Tablet disintegration was determined in the tablet disintegration tester. Six tablets from each brand were Ketoconazole. The absorbance was taken using the UV- spectrophotometer at a wave length of 238 nm2. The percentage content and milligram content of each of the samples was then determined and compared with the standard. The % of the assay calculated by following formula

% of the assay= (Absorbance of Brand/Absorbance of Standard) x100 (1)

Sr.no.	Brands	Average disintegration test
1	Amiketo 200	25% in 05 min 65% in 10 min 75% in 15 min 84% in 20 min
2	Ketowell 200	27% in 05 min 66% in 10 min 75% in 15 min 85% in 20 min
3	Dr.Zip 200	25% in 05 min 65% in 10 min 75% in 15 min 84% in 20 min

Table no. 6: Disintegration time of Ketoconazole table

Result and Discussion

The physical appearance of different brands of Ketoconazole

1. Weight Variation Test –

Weight variation of tablets is an important in-process control evaluation. The specification of this test is given in different pharmacopeias. The weight of a tablet being compressed is determined by the amount of granulation in the die prior to compression. For that reason, anything that can alter the die

filling process can alter the tablet weight and weight variation. Result of weight variation shown in table 3. According to the BP, the limit of weight variation test was, the average weight 130 mg or less the percentage difference should be ±10, more than 130 percentage differences should be ±7.5 and 324 mg and above percentage difference should be ±5. Regarding to the experimental result, average weight of all brands was more than 130 mg along with the percentage of differences comply with the limit

2. Hardness Test –

Hardness denotes the capability of a tablet to withstand mechanical shocks during handling in manufacturing, packaging and shipping. Tablet hardness, in turn, influences tablet density and porosity. It may affect tablet friability and disintegration time. It usually affects the drug dissolution and release and it may affect bio-availability. The acceptable range of hardness or crushing strength of tablet is 4 to 7 kg/f (kilogram of force). For all of the formulations, five tablets of each brand were taken and hardness of the tablets was determined. Regarding the results, average hardness for each brand was between 6 and 7 kg/f (Table 4). According to the limit for Monsanto hardness tester, brands of Ketoconazole comply with the specified limit.

3. Friability Test –

Friability is a tendency of the tablet to crumble. It is important for the tablet to resist attrition. For the duration of manufacturing and handling, tablets are subjected to stresses from collision and tablet sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from the tablet surface. Usually, friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. In this friability test, all brands showed impressive friability values. The friability values for ketoconazole tablet brands were ranged from 0 to 0.30%. For all brands, the percent (%) friability was less than 1% which ensures that all the tablets of each brand were mechanically stable

4. Disintegration Test

A drug to be absorbed from a solid dosage form after oral administration, it must be in solution, and the first important step towards this condition is usually the break-up of the tablet, it is well-known as disintegration. Simply, disintegration is the break down process of tablet into smaller particles and is the first step towards dissolution. The disintegration test is a measure of the time required under specific conditions for a group of tablets to disintegrateinton particles which will pass through a 10 mesh screen. In general, the test is useful as a quality assurance tool for conventional dosage forms. The rate of drug absorption as well as the therapeutic efficacy of the drug is dependent upon the disintegration time. If the disintegration time is not perfect we cannot state that effectiveness of the drug is good. The standard disintegration time for USP uncoated tablet must be as low as 5 minutes but majority of the tablets have a maximum disintegration time of 25-30 minutes. All brands comply with this limit (Table 6)

Conclusion

Although the physic-chemical examinations such as weight variation, friability, disintegration, dissolution were detected varying brand wise, but were found interior to defined limits. Being an over the-counter drug, the consumption of ketoconazole is too high. Therefore, it is important for each brand to be genuine, good manufactured and well marketed. So, additional exploration over the quality of ketoconazole is compulsory for safe human consumption

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