2026 Volume: 02 Issue: 06 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-21

PHARMACEUTICAL DEVELOPMENT AND REGULATORY DOCUMENTATION OF ITRACONAZOLE: A REVIEW FROM PRE-FORMULATION TO PRODUCT EVALUATION

***Akhisha M., Fathimath Hiba Parveen A.**

Department of Pharmaceutics, Malik Deenar College of Pharmacy, Seethangoli, Bela, Kasargod.

Article Received: 24 April 2026
Article Revised: 14 May 2026
Published on: 03 June 2026

***Corresponding Author: Akhisha M.**
Department of Pharmaceutics, Malik Deenar College of Pharmacy, Seethangoli, Bela, Kasargod.

DOI: https://doi-doi.org/101555/ijrpa.3671

1. ABSTRACT

Itraconazole is a broad-spectrum triazole antifungal agent widely used in the treatment of superficial and systemic fungal infections. Due to its poor aqueous solubility and variable bioavailability, formulation development of itraconazole requires detailed pre-formulation and evaluation studies to ensure efficacy, stability, and patient compliance. This review focuses on the pharmaceutical development and regulatory aspects of itraconazole formulations, particularly capsules. The study discusses the classification, mechanism of action, therapeutic uses, adverse effects, contraindications, and available formulations of itraconazole. It also highlights important pre-formulation studies including physicochemical characterization, solubility analysis, melting point determination, partition coefficient, micromeritic properties, compatibility studies, and stability studies. Evaluation of flow properties such as angle of repose, Carr's index, Hausner's ratio, bulk density, and tapped density was performed to assess powder behavior during formulation development. The review emphasizes the significance of pre-formulation data in optimizing dosage form design and ensuring quality, safety, and regulatory compliance of itraconazole products.

2.KEYWORDS: Antifungal agents, Itraconazole, pre-formulation studies, capsule formulation, capsule evaluation, pharmaceutical development, and regulatory documentation.

3.INTRODUCTION

Antifungal agents are drugs designed to combat fungal infections while sparing the human host from harm. Unlike antibiotics, the development of antifungal medications has progressed more slowly and for good reason. Bacteria are prokaryotic organisms with cellular structures and metabolic pathways that are very different from those of humans, making them easier targets for selective drug therapy. Fungi, however, are eukaryotes, sharing many cellular features with human cells. This close biological similarity makes it challenging to develop drugs that are deadly to fungi but safe for patients, as many antifungal compounds risk harming both. As a result, the search for effective and selective antifungal therapies has been a far more complex scientific challenge [3].

ITRACONAZOLE

INTRODUCTION

Itraconazole is a broad spectrum triazole antifungal agent. It has favorable pharmacodynamic and pharmacokinetic profiles and is available as both oral and iv. formulations. Over the last two decades, clinical and animal infection studies have demonstrated the efficacy of itraconazole in a wide range of superficial fungal infections[3].Itraconazole belongs to BCS class II. Itraconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 α demethylation via the inhibition of the enzyme cytochrome P450 14α-demethylase [3].

Itraconazole is a synthetic antifungal agent of the imidazole class; it works by slowing the growth of fungi that cause infection. It is used to treat fungal infection. Triazole drug targets the fungal-specific synthesis of membrane lipids [7].

Molecular formula: $C_{35}H_{38}C_{12}N_8O_4$

Molecular weight: 705.64g/mol

Chemical structure:

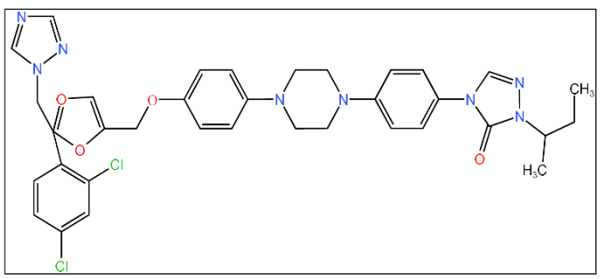

Fig.1: Chemical structure of Itraconazole.

MECHANISM OF ACTION:

Itraconazole is a synthetic triazole that exerts broad-spectrum antifungal activity by selectively inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14α-demethylase. This blockade disrupts the conversion of lanosterol to ergosterol, an essential component for fungal membrane stability. The resulting ergosterol depletion, combined with the accumulation of toxic 14α-methyl sterols, increases membrane permeability and leads to fungal cell death [14].

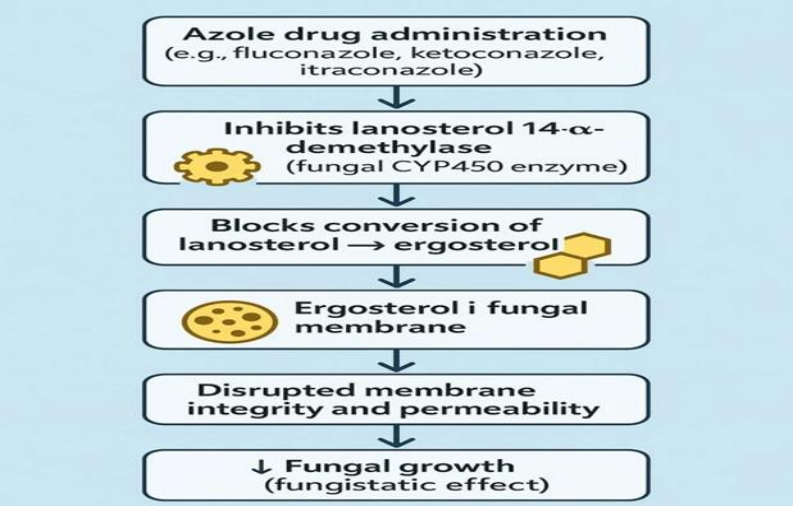

Fig.2: Pathway on mechanism of action of Itraconazole.

ADVERSE EFFECTS [14][13]:

- Congestive heart failure
- Renal failure
- Hepatopathy
- GI disturbance
- Dizziness
- Headache
- Hypokalemia
- Rashes
- Blood dyscrasias

CONTRAINDICATIONS [13]:

- Diabetes mellitus
- Hypertension
- Congestive heart failure

- Pregnancy
- Liver disease

USES [13]:

Used in treatment of:

- Cutaneous fungal infection
- Dermatophyte
- Candida onychomycosis
- Vaginal candidiasis
- Esophageal candidiasis

MARKETED FORMULATIONS:

1. Oral capsule:

Itraconazole Capsules were formulated utilizing the Solid Dispersion Technique with Drug Coating and Seal Coating Approach.

Doses available-65mg, 100mg, 130mg, 200mg

Brand names: ITRAPAR-100(Fig.3), CANDIFORCE-200, ITONAZ-100

Fig.3: Marketed Itraconazole oral capsule- Itrapar-100.

2. Oral solution:

Itraconazole oral solution is a liquid formulation designed to improve the bioavailability of this poorly water-soluble antifungal.

Doses available-10mg / ml

Brand names: ITRATUF, ITRAGIN

3. Intravenous injection:

Itraconazole IV injection is available for severe systemic infections.

Doses available: 10 mg/ml

Brand name: FUNGOSPOR

4. Topical cream:

Itraconazole cream is a topical antifungal medicine used to treat skin infections like ringworm, athlete's foot, jock itch, and yeast infections by stopping fungal growth.

Doses available:1% w/w

Brand name: CANDIRAP, ROTICOR

4.METHODS AND MATERIALS:

PREFORMULATION STUDIES OF ITRACONAZOLE CAPSULE

1. PHYSICOCHEMICAL PROPERTIES:

a) Organoleptic properties:

Organoleptic properties are the sensory characteristics specifically color, odor, taste etc., that are perceived by human senses (sight, smell, taste, touch, and sometimes hearing).

Table no. 1: Organoleptic properties and observation of Itraconazole.[5]

Sl. No.	Test	Observation
1.	Color	White
2.	Odor	Odorless
3.	Taste	Bitter

b) Solubility

Solubility is the maximum amount of a solute (solid, liquid, or gas) that can dissolve in a specific amount of solvent to form a stable, homogeneous solution at a given temperature and pressure.

Procedure [5]

Solubility of Itraconazole was determined in different media i.e. water, alcohol, dichloromethane etc. by “shake flask method”. Each glassware was then mixed with drug for 10 minutes using a vortex mixture. The mixture vials were then kept at 37± 1.0 in a shaker bath for 48 hours to get equilibrium. The equilibrated sample were removed from shaker and centrifuged at 5000rpm for 15 minutes to speared undissolved drug. Supernatant was taken and filtered through a 0.45m membrane filter. The concentration of API was determined in each solvent by UV spectrophotometer by scanning from 200-400nm.

Table no. 2: Solubility of Itraconazole in different media.

Sl. No.	Media	Inference
1.	Distilled water	Insoluble
2.	0.1N HCl	Insoluble

3.	Ethanol	Very slightly soluble
4.	Methanol	Very slightly soluble
5.	Dichloromethane	Freely soluble

c) Melting point

The melting point is the specific temperature at which a solid converts into a liquid at a given pressure, where both solid and liquid phases exist in equilibrium.

Procedure [5]

The melting point of the drug was determined by using capillary method. Itraconazole was filled in the capillary (10-15mm long and 1mm inside diameter) tube sealed at one end up to a height of approximate two mm from closed end and capillary was introduced into digital melting point apparatus. The temperature at which the drug melts was noted down as the melting point of the drug. The average of three values was considered as the melting point of drug.

Melting point of Itraconazole: **166.2°C**

d) Partition coefficient [5]

When a material is placed in an environment consisting of organic and aqueous phase, it gets distributed into two phases. The relative quantities that get distributed are expressed in the form of ratio known as partition co-efficient.

$$\text{Partition coefficient} = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}$$

Procedure

The partition coefficient of Itraconazole between n-octanol & water was determined by slight modification of "Shake Flask Method", at room temperature. Excess amount of drug was added in 10ml mixture of n-Octanol and water (1:1). The system was prepared in triplicate and was shaken gently in the separating funnel for 24 hours for achieving equilibrium. Then the two phases were separated and the concentration of drug in both phases was determined by UV spectroscopy and partition coefficient was calculated using the equation.

Table no. 3: Partition coefficient and nature of Itraconazole.

Drug	Partition coefficient	Nature
Itraconazole	5.50±0.98	Lipophilic

e) pH [4]

pH (potential of hydrogen) is a logarithmic scale from 0 to 14 measuring the acidity or alkalinity of an aqueous solution. A pH of 7 is neutral (e.g., pure water), less than 7 is acidic (higher H^+ concentration), and greater than 7 is alkaline/basic.

- Itraconazole is a weakly basic drug with a pKa of 3.7.
- pH-dependent solubility: Solubility is extremely poor at neutral pH and only increases in highly acidic environment.

f) Ionization constant (pKa)

An ionization constant (also known as a dissociation constant, denoted as K) is a quantitative measure of the extent to which a substance, such as an acid or base, dissociates into ions in a solution.

Itraconazole is a weakly dibasic compound characterized by a primary ionization constant of 3.7. Because of these values, the drug's solubility is strictly pH-dependent, meaning it requires a highly acidic environment (pH < 3) to become ionized and achieve dissolution [8].

2. MICROMERITIC PROPERTIES

a) Particle size [10]

The particle size of pure Itraconazole and Scanning Electron Microscopic (SEM) image of Itraconazole was determined using a microscope at 10x magnification.

The particle size of the pure Itraconazole powder was found to be 50 µm. The optical microscopic images of pure Itraconazole are shown in Fig. a and SEM image of pure Itraconazole Fig. b, respectively.

b) Flow properties

Flow properties and compressibility properties of drug powder were evaluated by measurement of angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio.

➢ **Angle of repose [2]**

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The angle of repose of granules was determined by funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The blends were passed through the funnel until it forms a heap. Further adding of granules was stopped as soon as the heap touches the tip of the funnel. A circle was drawn across it without disturbing the pile. The radius and height of the heap was noted down. The same procedure was repeated for

three times and the average value was taken. The angle of repose was calculated by using equation:

Angle of repose, $\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone respectively.

- **Bulk density [12]**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

Bulk density, $\rho_b = m/Vo$

Where, m= mass of solid particles

Vo= Total volume

- **Tapped density [12]**

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

Tapped density, $\rho_{tapped} = m/Vt$

Where, m= mass

Vt= Tapped volume

- **Compressibility (Carr's index) [2]:**

The flowability of powder can be evaluated by comparing the loose Bulk density and tapped bulk density of powder and the rate at which it packed down. Compressibility index of the granules was determined by the equation:

$$\text{Carr's index: } CI(\%) = \frac{(\rho_{tapped} - \rho_b)}{\rho_{tapped}} \times 100$$

Where, ρ_{tapped}= Tapped density

ρ_b= Bulk density

- **Hausner's Ratio [2]**

It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 –1.5, it was determined by the ratio of tapped density and bulk density.

Hausner's ratio, HR= Tapped density÷ Bulk density\

Table no. 6: Angle of repose, Carr's index, Hausner's ratio, bulk density and tapped density of Itraconazole. [10]

Parameter	Result
Angle of repose	47.46
Carr's index	33.33%± 0.14%
Hausner's ratio	1.35± 0.42
Bulk density	0.04± 0,03 g/cm^2
Tapped density	0.06± 0.06 g/cm^2

The powder showed poor flow properties as indicated by high angle of repose and Carr's index.

3. COMPATIBILITY STUDIES:

a) Fourier Transmission Infra-Red Spectroscopy (FTIR) [5]:

FTIR analysis studies was conducted for studying the compatibility and to determine if there are any possible drug excipients interactions. The prepared samples were scanned in the range from400cm^{-1} – 4000cm^{-1}.

Procedure:

FTIR spectrums of drug were obtained by means of a FTIR spectrophotometer. The samples were prepared by the potassium bromide disk method and measurements were attempted with the accumulation of 20 scans and a resolution of 4cm^{-1}over the range of 400-4000cm^{-1}. After running the spectra, significant peaks relating to major functional groups were identified; spectra of the subsequent sample of the same compound were compared with the original.

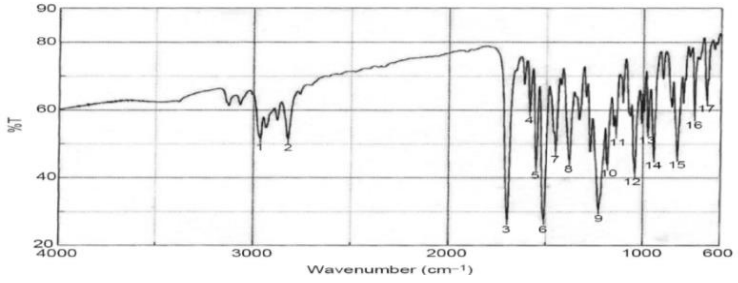

Fig.4: FTIR of Itraconazole.

Table no.7: Peaks and respective wavenumbers of itraconazole.

Sl. No	Functional Group	Wavenumber(cm^{-1})
1.	Aromatic CH Stretching	3130
2.	Aliphatic CH Stretching	2964
3.	C=O Stretching	1695.75
4.	C=N Stretching	1613
5.	C-N Stretching	1551
6.	C-Cl Stretching	700-850

b) Differential Scanning Calorimetry (DSC) [1]:

Differential scanning calorimetry (DSC) is now generally accepted as the technique of choice to determine the energetics of protein folding/ unfolding transitions and the thermodynamic mechanisms underlying those reactions.

Procedure:

4 mg of Itraconazole were hermetically sealed in a flat-bottomed aluminum pan and heated in the differential scanning calorimetry (DSC) instrument in an atmosphere of nitrogen at a flow rate of 20 ml/min. A temperature range of 20–200°C was used and the heating rate was 10°C/min.

The DSC results of Itraconazole are presented in Fig. 6. The first heating run shows an endothermic melting peak with its maximum at 169.47 °C.

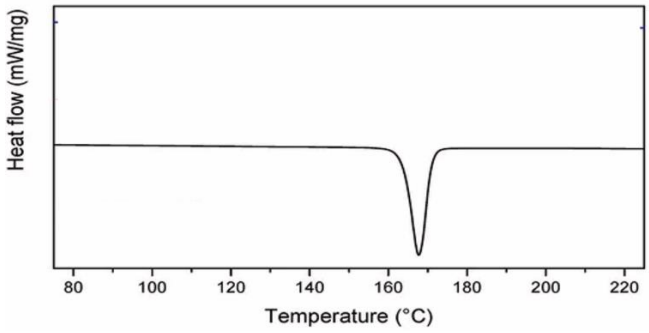

Fig.5: DSC of Itraconazole.

4. STABILITY STUDIES

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

a) Thermal stability

Thermal stability is a characteristic of a material to retain its structure and properties when exposed to higher temperatures.

Procedure [6]

Accelerated stability studies were conducted as per the ICH guidelines at 25±2˚C at 60±5% Relative Humidity at sampling intervals of 30, 60 and 90 days respectively. The drug content was determined periodically.

% Drug content determination of itraconazole was depicted in table no.8 and found that there was no significant change. At the first month of storage the drug content was found to be 87.48% and at the end of the third month it was found to be 86.21% at 25±2˚C and 60% RH. Therefore, we may conclude that the drug does not undergo degradation on storage.

Table no. 8: Percentage of Itraconazole content on 1st, 2nd and 3rd months of accelerated stability conditions.

Stability conditions	Percentage drug content per number of months		
	1	2	3
25±2˚C/60% RH	87.48	86.84	86.21

b) Photostability

The photostability of a drug substance may be defined as the response of the drug or drug product to the exposure to solar, UV, and visible light in the solid, semisolid, or liquid state that leads to a physical or chemical change.

Procedure [11]

Itraconazole is exposed in the solid state using the whole spectrum of UV-Visible radiation. The analyses were performed using high performance thin layer chromatography (HPTLC) technique with densitometric detection.

The result indicates considerable degradation of Itraconazole which could be clinically significant. After 72 hours of Itraconazole irradiation there remain less than 25%.

FORMULATION OF ITRACONAZOLE CAPSULES

Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word capsula, meaning a small container. Capsules are of two types:

- Hard gelatin capsules
- Soft gelatin capsules

COMPOSITION [18]:

Table no. 9: Ingredients used and their functions.

SL. No.	INGREDIENTS	FUNCTION
1.	Sugar spheres	Base pellet
2.	Itraconazole	Active Pharmaceutical Ingredient
3.	Hydroxy propyl methyl cellulose (HPMC)	Solubilizer
4.	Polyethylene glycol	Solubilizer
5.	Absolute ethanol	Solvent
6.	Dichloromethane	Solvent
7.	Talc	Glidant
8.	Colloidal silicon dioxide	Glidant
9.	Gelatin	Shell-forming agent
10.	Water	Plasticizer
11.	Titanium dioxide+ colorant	Opacifier

PREPARATION OF HARD GELATIN CAPSULE SHELL [16]:

Hard gelatin capsule shells are manufactured using a dip-coating method as follows:

Step 1: Preparation of the gelatin solution

Step 2: Dip-coating the gelatin solution on to metal

Step 3: Rotation of the dip-coated pins

Step 4: Drying of the gelatin-coated pins

Step 5: Stripping and trimming

Step 6: Joining of the trimmed capsule shell

Step 7: Printing

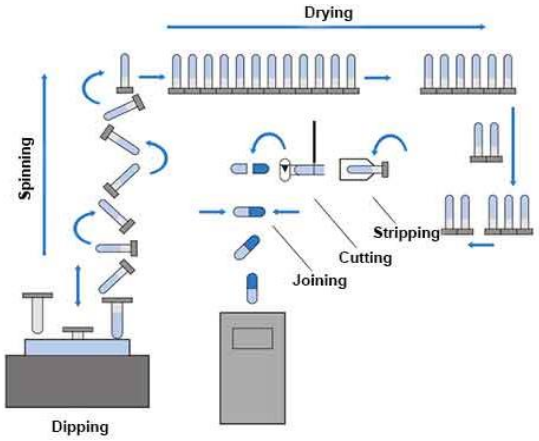

Fig. 6: Preparation of hard gelatin capsule shell.

Procedure:

Step 1: Preparation of the gelatin solution (dipping solution):

A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water which has been heated to 60–70°C in jacketed pressure vessels. To remove the air bubbles, a vacuum is applied to the solution.

Step 2: Dip-coating the gelatin solution on to metal pins (molds):

Dip pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan.

Step 3: Rotation of the dip-coated pins:

The bar containing the pins is removed and rotated several times to evenly distribute the solution around the pins.

Step 4: Drying of the gelatin-coated pins:

A blast of cool air is used to set the gelatin on the mold. At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Step 5: Stripping and trimming:

After the gelatin dried, the capsule is stripped off the mold and trimmed to the proper length.

Step 6: Joining of the trimmed capsule shell:

Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

Step 7: Printing:

After formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colors, containing information such as product name or code number, manufacturer's name or logo and dosage details.

PREPARATION OF CAPSULE FILL MATERIAL [15]:

1. Preparation of Drug Solution: Dissolve Itraconazole and a hydrophilic binder (HPMC) in an organic solvent mixture of Dichloromethane and Ethanol.
2. Inert Core Loading: Charge a fluidized bed granulator with inert sugar spheres.
3. Drug Layering: Spray the drug solution onto the preheated sugar spheres. The solvent evaporates, leaving a solid dispersion of Itraconazole in HPMC layered on the core.
4. Seal Coating (Optional): To prevent pellets from sticking and improve stability, apply a secondary layer of a polymer like Polyethylene Glycol (PEG).
5. Drying: Dry the coated pellets, often for several hours, to ensure residual solvent levels are within regulatory limits (e.g., loss on drying < 1%).

6. Capsule Filling: Blend the dried pellets with a lubricant (like talc) and fill them into hard gelatin capsules (usually size '0') to reach the target dose, such as 100 mg.

FILLING OF HARD GELATIN CAPSULES [16]:

- Rectification of capsules (placing empty gelatin capsules on the removable plate with bodies facing downward).
- Separation of caps from bodies.
- Dosing of fill material.
- Locking and packaging

Hard Gelatin Capsule Filling Machines [19]:

1. Manual/ hand-operated filler:

A manual capsule filling machine is mainly used for individual and small-scale capsule production, but it can also be used in industries requiring accurate filling. It can fill about 300 capsules in one operation using a 300-hole loading tray. The machine includes a powder tray, pin plate for sealing/filtering, and a cam handle for easy operation. Due to its simplicity, accuracy, and versatility, it is widely used in research laboratories, academic institutions, herbal/Ayurvedic preparations, pharmaceutical, cosmetic, food, veterinary, biotech, and small to medium-scale manufacturing industries.

2. Semi-automatic filler:

A semi-automatic capsule filling machine is a hybrid of manual and automatic machines. It requires less operator involvement and can automatically fill and arrange capsule caps through programmed controls while maintaining pharmaceutical hygiene standards. It can also be operated manually for small-scale production.

Its robust design makes it durable and low-maintenance. The machine can produce about 25,000–30,000 capsules per hour and is suitable for filling capsules of all sizes with powders, pellets, and granules.

3. Automatic filler:

Automatic capsule filling machines perform capsule separation, filling, and locking automatically without operator assistance. They improve production efficiency and reduce labor costs. Those advanced machines comply with current GMP standards and feature superior electronic controls and advanced loading systems. Their efficient separating system makes them compatible with capsules from suppliers worldwide.

(a) (b) (c)

***Fig. 7*: (a) Manual/ hand-operated filler, (b) Semi-automatic filler and (c) Automatic filler**

EVALUATION OF ITRACONAZOLE CAPSULES

1. GENERAL APPEARANCE [18]

a) Description:

White to off white granules containing opaque white (cap) and opaque white (body) colored capsules.

b) Size:

Capsule size = 0

2. DRUG CONTENT AND RELEASE

a) Weight variation test [20]

Procedure

20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight is noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weigh

b) Content uniformity test [20]

The amount of active ingredient should be within in the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount.

c) Disintegration test [20]

Disintegration of hard and soft gelatin capsules is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract.

Fig. 8: Disintegration test apparatus.

Procedure:

Place 1 capsule in each of the 6 tubes of the basket and suspend the assembly in water at 370℃±20℃, which is repeatedly immersed 30 times per minute. The capsules pass the test if no residue of drug or other than fragments of shell remains No.10 mesh screen of the tubes.

3. DISSOLUTION TEST [20]

Dissolution test for capsules drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test.

Procedure

Place 1000ml of water having a temperature of 36.50 to 37.50 in to the vessel. Place specified number of capsules in basket 7 adjust the speed to 100rpm.Withdraw the required volume for every 10-min time interval. Filter and determine the amount of active ingredient. Sample passes the test if the amount of active ingredients in the solution is not less than 70 % of the standard amount.

Fig. 9: Dissolution test apparatus.

4. MOISTURE PERMEATION TEST:

The USP requires determination of the moisture permeation characteristics of single-unit and unit dose containers to assure their suitability for packaging capsules.

Procedure [20]

The degree and rate of moisture penetration is determined by packaging the dosage unit together with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating absorption of moisture) and comparing the pre-test and post-test weight of the packaged unit.

5. STABILITY TESTING:

Stability tests for capsules are performed to known the integrity of gelatin capsule shell but not to know the stability of therapeutically active agent and for determining the shelf life of capsules.

Procedure [20]

The capsule shells must be equilibrated to known atmospheric conditions with relative humidity of about 20-30% at 21℃-24℃. The capsules must be used for further tests only after re-established the equilibrium at room temperature.

PACKAGING OF ITRACONAZOLE CAPSULES:

Table no. 11: Types of packaging of Itraconazole capsules.

Type of packaging	Description
Primary packaging	✓ **Strip packs:** hermetically sealed (aluminum foil/plastic) ✓ **Blister packs:** capsules enclosed in pre-formed cavities
Secondary packaging	Carton box
Tertiary packaging	Bulk shipper cartons/pallets

(a) (b)

Fig. 10: (a) Strip pack of Itraconazole capsules & (b) Blister pack of Itraconazole capsules

STORAGE OF ITRACONAZOLE CAPSULES [20]

Storage for hard gelatine capsules should be 240℃ to280℃.The moisture content exceeding between 12-15%. When the capsules are stored at high humidity, it may absorb the moisture content and it may lose it shape.at low humidity they loss the water from the shell and they

become brittle. The ambient humidity and temperature levels for storage of hard gelatine capsules are as follows,

Minimum=35%RH, 150℃

Best possible =50%RH, 200℃

Maximum=65%RH, 250℃

LABELLING REQUIREMENTS OF ITRACONAZOLE CAPSULES:

- Name of preparation
- Strength and dosage form
- Quantity
- Ingredients
- Instructions for use:
  - *Taken immediately after a full meal*
  - *Do not chew, crush or cut capsules*
- Precautions and warnings
  - *Keep out of reach of children*
- Registration number
- Batch number
- Manufactured and expiry dates
- Price
- Manufacturer's name and address

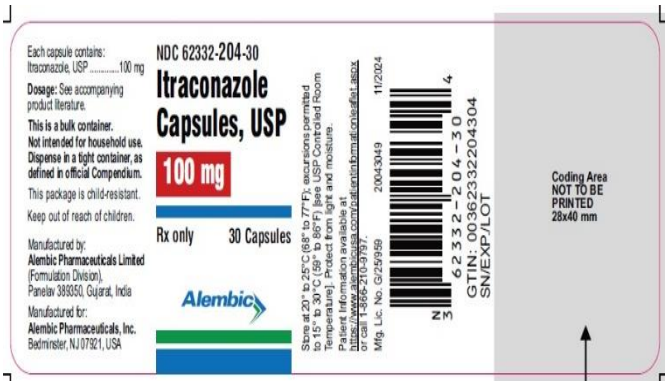

Fig. 10: Label of Itraconazole capsules

REGULATORY DOCUMENTATION OF ITRACONAZOLE CAPSULES:

FDA Approval Pathways:

1. NDA (New Drug Application):
2. Used for new drugs.

Example: *Sporanox* was approved (in 1992) for treating fungal infections.

3. ANDA (Abbreviated New Drug Application):

Used for generic drugs (approved in late 1990s-2000s).

Must show they work the same as the original drug (bioequivalence).

Tested under fasting and fed conditions.

4. 505(b)(2) Pathway:
5. Used for modified or improved versions of existing drugs.

Example: *Tolsura capsules* (approved in 2018) (better absorption). Uses already available safety and efficacy data.

WHO Prequalification

Ensures quality, safety, and effectiveness of medicines globally.

Example: Itraconazole 100 mg capsules are checked to meet international standards.

8.REFERENCE:

1. Sinhal A, Wagh R. Formulation and Evaluation of Lipid-based Nano formulation of Itraconazole. International Journal of Drug Delivery Technology. 2024;14(1):417-42
2. Manesh G. Bhisei, Amol R. Lehane, Nitin B. Kohale, Shailesh G. Shende. A Review on Pre formulation Studies. Journal of Emerging Technologies and Innovative Research. February 2022;9(2):609-625
3. Sangita P. Shirsat, Kaveri P. Tambe, Ganesh G. Dhakad, Paresh A. Patil, Ritik. S. Jain. Review on Antifungal Agents. Research Journal of Pharmacology and Pharmacodynamics. 2021;13(4):147-4
4. Lee JH, Park C, Weon KY, Kang CY, Lee BJ, Park JB. Improved Bioavailability of Poorly Water-Soluble Drug by Targeting Increased Absorption through Solubility Enhancement and Precipitation Inhibition. Pharmaceuticals (Basel). 2021 December 2;14(12):1255
5. Mr. Pankaj Kumar, Dr. Amit Chaudhary, Mr. Ajay Singh, Dr. Abhishek Soni. Pre formulation Study of Itraconazole for Novel Drug Delivery System Formulation. International Journal of Research and Analytical Reviews. November 2020;7(4):953-962

6. Vineetha Taadi, Tripura Sundari. I, Dr. Bhagawan Raju M. Formulation and evaluation of itraconazole oral cubosomal capsules. International Journal of Pharmaceutical Sciences Review and Research. December 2019; 59(2):58–66
7. Poonam Madhukar KASAR, Kalyanisundarrao Kale, Dipti Ganesh Phadthare. Formulation and Evaluation of Topical Anti-fungal Gel Containing Itraconazole. June 2018;10(4):71-74
8. Stevanus Hiendrawan, Bambang Veriansyah, Raymond R. Tjandrawinata. Solid-State Properties and Solubility Studies of Novel Pharmaceutical Cocrystal of Itraconazole. International Journal of Applied Pharmaceutics. 2018;10(5): 97-104
9. Gita Chaurasia. A review on pharmaceutical pre formulation studies in formulation and development of new drug molecules. International Journal of Pharmaceutical Sciences and Research. June 2016;7(6)2313-20
10. Janki Fadke, Jagruti Desai, and Hetal Thakka. Formulation Development of Spherical Crystal Agglomerates of Itraconazole for Preparation of Directly Compressible Tablets with Enhanced Bioavailability. AAPS Pharma Science Tech. December 2015;16(6): 015-332
11. Ekiert Radostaw, Krzek Jan. Photostability of triazole antifungals in the solid state. Current Issues in Pharmacy and Medical Sciences. 2013;26(3):365-378
12. J P Sousa e Silva, D Splendor, I M B Goncalves, P Costa, J M Sousa Lobo. Note on the Measurement of Bulk Density and Tapped Density of Powders According to the European Pharmacopeia. AAPS Pharm SciTech. July 2013;14(3):1098–110
13. Susan M. Grant & Stephen P. Clissold. Itraconazole: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Superficial and Systemic Mycoses. Springer Nature. October 2012;37(6):310–344
14. Nafsika H. Georgopapadakoui, Thomas J. Walsh. Antifungal Agents: Chemotherapeutic Targets and Immunologic Strategies. Antimicrobial Agents and Chemotherapy. February 1996;40(2): 279-291
15. Suresh Kolli, K. Vijaya Sri, P. N. Murthy, V. R. Sirisha. K. Solubility Enhancement of Itraconazole by Hypromellose Formulated by Solution-Suspension Layering Technique. Research J. Pharm. and Tech 2018; 11(11): 4850-4853
16. Satish P. Mohitkar, Sanchit V. Akhare, Bhagyashree D. Balpande. Detailed Study of Formulation and Evaluation of Capsule Dosage Form: A Review. International Journal of Pharmaceutical Research and Applications. 2023;8(3): 1590-1599
17. Rajan Verma, Shrikant Hodge, Chandrashekhar Gargote, Prakash Modi, Naresh Upreti,

Lokesh Yadav, Raviraj Pillai. Assessment of physical and dissolution characteristics of various itraconazole capsule formulations: a comparative analysis.

18. International Journal of Research in Dermatology. 2019Nov;5(4):765-770
19. Shinde NK, Mane DV. Manufacturing Process Optimization of Anti-fungal Drug Product Itraconazole Capsules by Wet Granulation Approach. Frontiers in Health Informatics. 2024; 13(4): 1513-1536
20. Mr. Akash Dinakar Surve, Miss. Aishwarya Santosh Kaware, Mr. Abhishek Shreedhar Chaudhari, Mr. Akshay Gajanan Rajguru, Prof. Dr. Abhinay Kumar Dwivedi. Review on Capsule Filling Machines. International Journal of Advanced Research in Science, Communication and Technology. December 2023; 3(2): 2581-9429
21. S. Gousia Begum, Y. Hasmitha, U. Girija Reddy, M. Deepa, K. Supraveena Reddy, R. Susmitha. A review on manufacturing and evaluation of capsules. World Journal of Pharmaceutical Sciences. 2018; 6(8):98-105.
22. Mohitkar, Sanchit V. Akhare, Bhagyashree D. Balpande. Detailed Study of Formulation and Evaluation of Capsule Dosage Form: A Review. International Journal of Pharmaceutical Research and Applications. 2023;8(3): 1590-1599.