CHAPTER–4
DRUG AND EXCIPIENT PROFILE

DRUG PROFILE:\textsuperscript{86}:

Terbinafine hydrochloride is a potent anti-fungal agent of the allylamine. Allylamines are synthetic derivative of 3-aminopropene. This drug has broad spectrum activity in \textit{in vitro} against yeast, dimorpine fungi, dematiaceous fungi, moulds dermatophytes, etc. This drug act both as fungicidal and fungistic as per concentration\textsuperscript{87}.

Chemical Name\textsuperscript{88}: [(2E)-6,6-dimethylhept-2-en-4-yn-1-yl (methyl) (naphthalene-1-ylmethyl)amine.

Chemical structure\textsuperscript{89,90}:

\[
\text{Molecular formula}\textsuperscript{91}: \text{C}_{21}\text{H}_{25}\text{N}
\]

\[
\text{Molecular weight}\textsuperscript{91}: 327.90 \text{ gm/ml.}
\]

\[
\text{Description}\textsuperscript{93}: \text{White/ off-white crystalline powder.}
\]

\[
\text{Melting point}\textsuperscript{93}: 204-208\degree\text{C}
\]

\[
\text{Solubility}\textsuperscript{92}: \text{Slightly soluble in water, acetone, freely soluble in methanol, chloroform and ethanol, partially insoluble in hexane.}
\]

\[
\text{Odour}: \text{Odourless}
\]

\[
\text{Storage}\textsuperscript{96}: \text{Terbinafine HCl should be stored at 25\degree\text{C} in a tight container, protected from light.}
\]

\[
\text{Category}\textsuperscript{94}: \text{Trypanocidal agent, anti-fungal, allylamine.}
\]
Loss on Drying\textsuperscript{93}: 0.5\% max.
Residue on ignition: 0.10\% max.
PH\textsuperscript{91}: 2.5\textasciitilde3.8.
Heavy metals: \leq20 ppm max.

Mechanism of Action\textsuperscript{97}:

Terbinafine HCl act by inhibiting squalene epoxidase which plays a key role in ergosterol biosynthesis and this enzyme is essential component of fungal cell membrane. Terbinafine HCl also leads to accumulation of toxic amounts of squalene resulting in death of fungal cell.

Pharmacodynamic Properties\textsuperscript{98}:

Terbinafine HCl has broad spectrum of antifungal activity. At low concentration it is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity against yeast in fungicidal/fungistatic depending on the species.

Pharmacokinetic Properties\textsuperscript{92,98,99}:

Absorption: Terbinafine HCl is well absorbed (75\% orally).
Bioavailability: 40\% because of first pass hepatic metabolism. Less than 5\% of topical dose of drug is absorbed.
Metabolism: Liver
Excretion: In urine 80\% and feces 20\%.
Protein binding: >99\%
Half-life: 16-17 hr
Peak plasma concentration: 0.97 mg/ml within 2 hr.

Drug Interactions\textsuperscript{100}:

No evidence of accumulation with other drug is seen. The plasma clearance of drug may be increased by drugs which induce
metabolism (rifamicin) and may be inhibited by drugs which inhibit cytochrome P-450 (cimetidine). Drug alone does not inhibit cytochrome P-450. Rifamicin decreases blood levels of drug, cimetidine increases blood levels of drugs. Terbinafine shows negligible potential to inhibit or reduce clearance of drugs that are metabolized via other cytochrome P-450 enzymes e.g., cyclosporin, tolbutamine, triazolam, oral contraceptives.

**Adverse Effects**\(^{101}\): Gastric upset, rashes, taste-disturbance some cases of hepatic dysfunction and the haematological disorders, erythema, rashes, itching, irritation, urticaria, headache, nausea, diarrhoea, abdominal pain, Stevens-Johnson’s syndrome, neutropenia can also be seen.

**Therapeutic Uses**: Fungal infection of skin and nails caused by trichophyton e.g., trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton verrucosum, Trichophyton violaceum, microsporum canis and epidermophyton floccosum. Also indicated in Tinea pedis, Tinea corporis, Tinea cruris, Tinea capitis and Pityriasis, Tinea versicolor. Onychomycosis can also be treated

**Precautions**: Cases of cholestasis and hepatitis have been reported. This usually occurs within two months of starting treatment. If patient present with signs or symptoms suggestive of liver dysfunction, such as pruritis, fatigue, abdominal pain, nausea, anorexia, tiredness, jaundice, vomiting or dark urine, pale stool, hepatic origin should be verified and drug therapy should be discontinued. Patients with impaired renal function (creatinine clearance) less than 50 ml/ min or serum creatinine of more than 300 mmol/l should receive half the normal dose.
**Preparation and Dose**: \(^{102,103}\)

Terbinafine HCl is available in the form of tablet, creams.

- Terbinafine HCl tablets ..........125 mg, 250 mg
- Terbinafine HCl cream ............1% w/w

2-6 weeks of treatment is required according to the site and according to the infection due to organism. 250 mg of tablet should be taken daily for 6 weeks suffering from finger-nail onychomycosis and for 12 weeks in case of toe-nail onychomycosis. The usual duration of treatment for fungal or yeast skin infection has been 2-4 weeks (topical therapy) but shorter courses of topical terbinafine (1-2 weeks) were as effective as standard duration therapy in dermatomycoses. Terbinafine is used topically for dermatophyte infection of skin and orally for infection of hair and nails. Tinea pedis, Tinea cruris, Tinea corporis – topically applied bid for 1-4 weeks.

**Excipient Profile**\(^ {104}\)

**Starch**

Non-proprietary name:

- BP – Maize starch, potato starch
- USPNF: Corn starch, potato starch.

**Biological source of starch:**

Starch of pharmaceutical use consists of polysaccharide granules obtained from the caryopsis of maize or corn, zea meys linn family Gramineae. Potato starch obtained from solanum tuberosum linn family solanaceae.

**Synonyms:** Amido, amidon, amilo, amyllum and pharm gel.
**Chemical name:** Starch  
**Empirical formula:** \((\text{C}_6\text{H}_{10}\text{O}_5)_\text{n}\); \(n = 300 – 1000\).  
**Molecular weight:** 50,000 – 1,60,000  
Starch consists of amylose and amylopectin, two polysaccharides based on \(\alpha\)-glucose.  
**Functional category:** Glidant, tablet and capsule diluent, tablet and capsule disintegrant, tablet binder.  
**Description:** Starch occurs as an Odourless and tasteless, fine, white-colored powder comprising very small spherical or avoid granules whose size and shape are characteristic for each botanical variety.  
**Typical properties**  
Acidity/ Alkalinity: pH – 5.5 to 6.5 for a 2% w/v aqueous dispersion of corn starch at 25ºC.  
Bulk density: 0.462 g/cm\(^3\) for corn starch  
Tapped density: 0.658 g/cm\(^3\) for corn-starch  
True density: 1.478 g/cm\(^3\) for corn starch  
Flowability: 10.8 – 11.7 g/s for corn starch. Corn starch is cohesive and has poor flow characteristics.  
Gelatinization temperature:  
73ºC for corn starch  
72ºC for potato starch  
**Moisture content:** All starches are hygroscopic and rapidly absorb atmospheric moisture.  
**Particle size distribution:**  
Corn starch: 2 to 32 \(\mu\)m  
Potato starch: 10 to 100 \(\mu\)m  
Median diameter for corn starch is 17 \(\mu\)m.
**Solubility:** Practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5-10% at 37°C.

**Specific surface area:**
For corn starch: 0.41 to 0.43 m²/g
For potato starch: 0.12 m²/g

**Swelling temperature:**
65°C for corn starch
64°C for potato starch

**Uses of starch:**
1. Starch is widely used as an excipient in pharmaceutical formulation, particularly oral tablets.
2. Starch is an edible food substance and is generally regarded as an essentially non-toxic and non-irritant material.
3. Starch is used as a binder, diluent and disintegrant in oral solid dosage formulation.
4. Starch is used as poultice.
5. A starch suspension may be swallowed as an antidote for iodine poisoning.