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ANALYTICAL METHODOLOGIES FOR DETERMINATION OF ITRACONAZOLE AND TERBINAFINE HCL IN BULK AND PHARMACEUTICAL DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

Itraconazole is one of the triazole antifungal agent used in treatment of fungal infection. Itraconazole inhibits cytochrome P-450-dependent enzyme resulting in impairment of ergosterol synthesis. Terbinafine Hydrochloride is synthetic allylamine antifungal agent inhibit synthesis of ergosterol by inhibiting fungal squalene monooxygenase (squalene 2,3-epoxidase), an enzyme that is a part of fungal cell wall synthesis pathway. The most commonly adopted methods for determination both drugs are UV-Visible Spectroscopy, HPLC (High Performance Liquid Chromatography), RP-UPLC (Reverse Phase-Ultra Performance Liquid Chromatography), HPTLC (High Performance Thin Layer Chromatography). This article provides critical review on the methodologies available for qualitative and quantitative determination of Itraconazole and Terbinafine HCL in bulk and pharmaceutical dosage forms.

KEYWORDS: Antifungal, Itraconazole, Terbinafine Hydrochloride, RP-UPLC, HPTLC, RP-HPLC, UV-Spectroscopy.

INTRODUCTION

The fungal kingdom includes yeasts, molds, rusts and mushrooms. Fungi like animals, are heterotrophic, i.e. they obtain nutrients from the environment and not from endogenous sources. Some of these fungi are pathogenic and can produce mild to severe fungal infection. An antifungal agents is a drug that selectively eliminates fungal pathogens from a host with minimal toxicity to the host.[1]

Itraconazole is an triazole derivative antifungal agent. Chemically it is (1-(butan-2-yl)-4-{4-[4-(4-{[2R,4S)-2-(2,4-dichlorophenyl-2-(1H-1,2,4-triazole-1-ylmethyl)1,3-dioxolan4yl] methoxy} phenyl) piperazin-1-yl] phenyl}4,4-dihydro-1H-1,2,4-triazole-5-one). It is used for the inhibition of fungal cytochrome p450 enzyme "lanosterol 4 demethylase", used in conversion of lanosterol to ergosterol, which is a main sterol in fungal cell membrane, thus inhibits replication and promotes cell death in case of the yeast cell transformation into hypothetically invasive hyphae. The empirical formula of Itraconazole is $C_{35}H_{38}Cl_2N_8O_4$ and its molecular weight is 705.633.[2] Chemical structure is shown in fig.1.

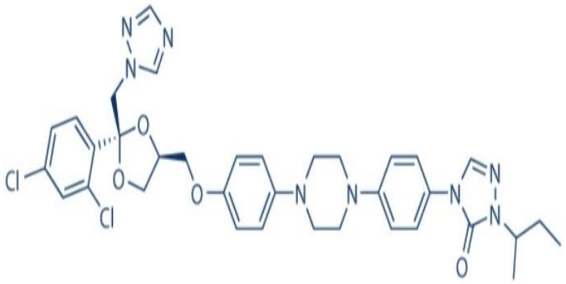

Figure 1: Itraconazole.

Terbinafine Hydrochloride is an allylamine antifungal agent and acts by inhibiting squaleneepoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membrane. Chemically it is (2E)-N,6,6-trimethyl-N-(naphthalene-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride. The empirical formula Terbinafine Hydrochloride is $C_{21}H_{25}N.HCl$ and its molecular weight is 327.92.(3) Chemical structure is shown in fig.2.

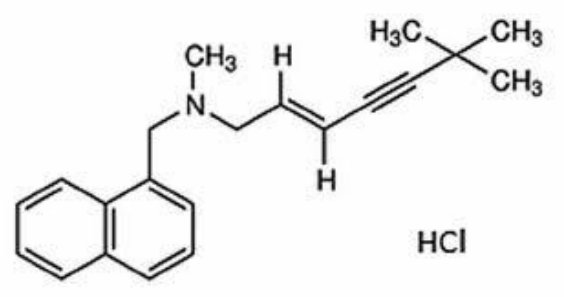

Figure. 2: Terbinafine Hydrochloride.

Reported methods are categorized depending on the following considerations

1. Methods for determination of Itraconazole single and combination with other drugs by UV-Spectroscopy, chromatography and other techniques.
2. Methods for determination of Terbinafine Hydrochloride single and combination with other drugs by UV-Spectroscopy, chromatography and other techniques.

Table. 1: Methods For Determination of Itraconazole Single & Combination with Other Drugs by UV-Spectroscopic, Chromatographic & Other Techniques.

SR.NO.	DRUGS	METHOD	DESCRIPTION	REF.NO.
1.	**Itraconazole In bulk and formulation**	**UV-Visible Spectrophotometry**	**Detection wavelength** - 262nm **Solvent**- Methanol **Linearity Range** - 4-14µg/ml **Regression Coefficient**- 0.9982 **%Recovery**- 99.11-101.18% **LOD**- 0.146µg/ml **LOQ**- 0.443µg/ml	[4]
2.	**Itraconazole In Bulk and Capsule**	**UV-Visible Spectrophotometry**	**ZERO ORDER DERIVATIVE** **Detection Wavelength** – 255nm **Solvent** – Phosphate Buffer (pH 2.0) **Linearity Range** – 5.0-60.0 µg/ml **Regression Coefficient**-0.999 **%Recovery**- 98.59% **LOD** – 0.39µg/ml **LOQ** – 1.19µg/ml **FIRST ORDER DERIVATIVE** **Detection Wavelength** – 270nm **Solvent** – Phosphate Buffer (pH 2.0) **Linearity Range** – 5.0-60.0 µg/ml **Regression Coefficient** -0.999 **%Recovery**- 99.17% **LOD** – 0.66µg/ml **LOQ** – 2.01µg/ml	[5]
3.	**Itraconazole In Bulk and Capsule Formulation**	**UV-Visible Spectrophotometry**	**Detection Wavelength** – 262nm **Solvent** – Acidic Ethanol **Linearity Range** – 2-12µg/ml **Regression Coefficient**-0.996 **%Recovery**- 0.53% **LOD –** 0.785µg/ml **LOQ –** 2.38µg/ml	[6]
4.	**Itraconazole**	**UV-Visible Spectrophotometry**	**Detection Wavelength** – 261nm **Solvent** – Methanol **Linearity Range** – 2.5-25 µg/ml **Regression Coefficient** -0.999 **%Recovery**– 98.546%	[7]
5.	**Itraconazole**	**UV-Visible Spectrophotometry**	**Detection Wavelength** – 267nm **Solvent** - Chloroform **Linearity Range** – 1-10 µg/ml **Regression Coefficient** -0.999 **LOD –** 0.14µg/ml **LOQ –** 0.43µg/ml	[8]

6.	**Itraconazole In Tablet Dosage Form**	**HPLC**	**Detection Wavelength** – 260nm **Column** - Hypersil/C_{18} **Mobile Phase** - ACN: 0.1%Triethyiamine (90:10) **Linearity Range** – 1.0-100µg/ml **Regression Coefficient** - 0.9972 **Flow Rate** - 1.0ml/min **Injection Volume** - 10µL **RetentionTime** - 4min **Detector** – UV Detector **LOD**– 0.3µg/ml **LOQ** – 1.0µg/ml	[9]
7.	**Itraconazole In Bulk and Capsule Formulation**	**RP-HPLC**	**Detection Wavelength** – 264nm **Column –** C18G **Mobile Phase** – ACN:0.1%Acetic Acid (50:50) **Linearity Range** – 10-60µg/ml **Regression Coefficient** -0.996 **Flow Rate** – 1.0ml/min **Injection Volume** – 20µl **Retention Time** – 3.44min **LOD** – 0.4389µg/ml **LOQ** – 1.341µg/ml	[10]
8	**Itraconazole In Bulk & Marketed Formulation**	**HPLC**	**Detection Wavelength** – 263nm **Column** –HiQSil C18-HS **Mobile Phase** – ACN: Double Distilled Water (90:10) **Linearity Range** – 5-60µg/ml **Regression Coefficient**-0.991 **Flow Rate -**1.0ml/min **Injection Volume -**20µl **Retention Time** – 7.75min **Detector** – UV Detector **LOD** – 0.3356µg/ml **LOQ** – 1.1657µg/ml	[11]
9.	**Itraconazole In Capsule Dosage Form**	**RP-HPLC& UV**	**Detection Wavelength** – 225nm **Column** – Inertsil C18 **Mobile Phase** – Tetrabutyl Ammonium Hydrogen Sulphate Buffer:ACN (40:60) **Linearity Range** – 50-200µg/ml **Regression Coefficient** -0.9993 **Flow Rate** – 1.5ml/min **Retention Time** – 5.617min **Tailing Factor** – 1.08 **% Recovery** – 98.3% **LOD** – 0.85µg/ml **LOQ** – 2.60µg/ml	[12]
10.	**Itraconazole In Pure & Pharmaceutical Dosage Form**	**RP-HPLC**	**Detection Wavelength** - 306nm **Column** – DionexC_{18} **Mobile Phase**– MeoH:PotassiumDihydrogen Phosphate Buffer (pH 7.5) (40:60) **Linearity Range** – 200-600µg/ml **Regression Coefficient** -0.999 **Flow Rate** - 1.5ml/min **Injection Volume –** 10µL **Retention Time** – 5.2min **Detector** – UV **Tailing Factor** – 1.138	[13]

			LOD Column– Inertsil ODS – C18 **Mobile** – 1.8594µg/ml **LOQ** – 6.197µg/ml	
11.	**Voriconazole & Itraconazole In Tablet Dosage Form**	**HPLC**	**Detection Wavelength** – ITZ :306nm, VOZ:256nm **Phase** – ITZ - Buffer (pH 5):MeoH (20:80) VOZ – Water:MeoH (80:20) **Linearity Range**– ITZ: 10-30µg/ml VOZ: 10-30µg/ml **Regression Coefficient** - ITZ:0.9993 VOZ : 1 **Flow Rate** - 1ml/min **Injection Volume** - 20µL **Retention Time** – ITZ:1.671min VOZ:5.050min **LOD** – ITZ : 1.091128934µg/ml VOZ : 0.150726233µg/ml **LOQ** – ITZ : 3.306451315µg/ml VOZ : 0.456746161µg/ml	[14]
12	**Itraconazole In Capsule Dosage Form**	**RP-HPLC**	**Detection Wavelength** - 225nm **Column**– ThermoHypersil BDS C18 **Mobile Phase** – Buffer:ACN (65:35) **LinearityRange**– 10-200µg/ml **Regression Coeficient**-0.9999 **Flow Rate** - 1.5ml/min **Injection Volume** - 10µL	[15]
13.	**Itraconazole and Hydroxyitraconazole**	**HPLC**	**Detection Wavelength** – 258nm **Column** –Lichrospher 10RP8 **Mobile Phase** - ACN:Water (62:38)(pH 6) **Extraction Solvent** – Heptane:Isoamylalcohol (90:10) **Linearity Range–** 0.1-3.2µg/ml **Regression Coefficient** – ITZ : 0.9999 HITZ : 0.9999 **Flow Rate** – 2.0ml/min **LOD** – ITZ : 10µg/ml HITZ : 7µg/ml	[16]
14.	**Itraconazole In Capsule Dosage Form**	**Stability Indicating RP-UPLC**	**Column** – Accquity BEH C18 **Mobile Phase** – A) Buffer:Tetrahydrofuran (95:5 pH 2.5) B) ACN **LinearityRange**– 25-150µg/ml **Regression Coefficient** -0.99987 **Flow Rate** – 0.40ml/min **Retention Time** – 8min	[17]

Table No: 2 Methods For Determination of Terbinafine Hydrochloride Single & Combination With Other Drugs by UV-Spectroscopic, Chromatographic & Other Techniques.

SR.NO.	DRUGS	METHOD	DESCRIPTION	REF.NO.
15.	**Terbinafine HCL In Tablet Dosage Form**	**UV-Visible Spectrophotometry**	**Detection Wavelength** - 223nm **Solvent** – 0.1N HCL **Linearity Range** – 1-3.5µg/ml **Regression Coefficient** – 0.995 **%Recovery** - 99.16-100.75% **LOD –** 0.086µg/ml **LOQ** – 0.260µg/ml	[18]
16.	**Terbinafine In Bulk & Formulation**	**UV-Visible Spectrophotometry**	**Detection Wavelength –** 283nm **Solvent -** Water **Linearity Range –** 5-30µg/ml **Regression Coefficient –** 0.999 **LOD –** 1.30µg/ml **LOQ –** 0.42µg/ml **% Recovery –** 98.54-99.58%	[19]
17.	**Terbinafine HCL In Dosage Form**	**UV-Visible Spectrophotometry**	**Detection Wavelength** – 224nm **Solvent** - Methanol **Linearity Range** – 0.8-2.8µg/ml **RegressionCoefficient** – 0.9997 **% Recovery** – Cream : 102.00% Tablet : 99.90% **Volumetric Method** **Titration Solvent** – 0.05M Perchloric Acid **Indicator** – Crystal Violet **% Recovery** – 100.41-101.18%	[20]
18.	**Terbinafine HCL In Dosage Form**	**Stability Indicating UV Spectrophotometric Assay**	**Method – A** **Detection Wavelength** - 222nm **Solvent** - 0.1M HCL **Linearity Range** – 0.2-2.0µg/ml **Regression Coefficient** -0.9999 **%Recovery** – 100.19% **LOD** – 0.003µg/ml **LOQ** – 0.01µg/ml	[21]
19.	**Terbinafine HCL In Pure & Tablet Dosage Form**	**Spectrophotometric Method**	**Detection Wavelength** – 282nm **Solvent** – 282nm **Linearity Range** – 8-24µg/ml **Regression Coefficient** – 0.998 **%Recovery -** 99.82-100.2% **LOD** – 0.35µg/ml **LOQ** – 0.81µg/ml	[22]
20.	**Terbinafine HCL & Mometasone Furoate In Combined Dosage Form**	**UV Spectrophotometry**	**DetectionWavelength** – TH:282nm MF:248nm **Solvent** – Methanol **Linearity Range** – TH : 10-70µg/ml MF : 1-7µg/ml **RegressionCoefficient** – TH: 0.999 MF :0.998 **LOD** – TH : 0.50µg/ml MF : 0.105µg/ml **LOQ** – TH : 1.67µg/ml MF : 0.318µg/ml **%Recovery** – TH : 100.68-101.43% MF : 98.64-100.08%	[23]

21.	**Terbinafine HCL & Telmisatran**	**UV-Visible Spectrophotometry**	**Detection Wavelength –** TH : 610nm Tel : 610 nm **Solvent** – TH : Distilled H_2O Tel : 0.2M NaoH **Linearity Range** – TH : 2-16 µg/ml Tel : 4.-128µg/ml **Regression Coefficient** – TH : 0.9999 Tel : 0.9996 **LOD** – TH : 0.65µg/ml Tel : 13µg/ml **LOQ** – TH : 1.96µg/ml Tel : 39.3µg/ml	[24]
22.	**Terbinafine HCL & Mometasone Furoate In Combined Dosage Form**	**RP-HPLC**	**Detection Wavelength** – 248nm **Mobile Phase** – MeoH:Water (95:5) **Column** – C18 **Detector** – PDA **Linearity Range** – TH : 20-200µg/ml MF : 2-20µg/ml **Regression Coefficient** – TH : 0.999 MF : 0.999 **Retention Time** – TH : 6.9min MF : 3.2min **LOD** – TH : 5.57µg/ml MF : 0.07µg/ml **%Recovery** – TH : 101.18% MF : 99.67	[25]
23.	**Terbinafine HCL & Bezafibrate In Pharmaceutical Dosage Form**	**RP-HPLC**	**Column** – C18 **Flow Rate** – 1.0ml/min **Injection Volume** - 20µl **Terbinafine Hydrochloride** **MobilePhase** – MeoH:H_2O:Ammonium Dihydrogen Phosphate (60:15:25) **Detection Wavelength** – 225nm **Linearity Range** – 2-12µg/ml **Regression Coefficient** – 0.999 **Retention Time** - 5.1min **LOD** - 0.5µg/ml **LOQ** - 0.15µg/ml **%Recovery** – 99.51% **Bezafibrate** **Mobile Phase –** MeoH:ACN:Orthophosphoric Acid (35:55:10) **Detection Wavelength** – 232nm **Linearity Range**- 0.2-1.4µg/ml **Regression Coefficient** – 0.996 **Retention Time** - 6.0min **LOD** – 0.01µg/ml **LOQ** – 0.04µg/ml **%Recovery** – 99.94%	[26]
24.	**Terbinafine HCL & Mometasone Furoate In Combined Dosage Form**	**RP-HPLC**	**Column –** Enable C18 **Mobile Phase -** ACN:0.1% Orthophosphoric Acid (67:33) pH3 **DetectionWavelength** – 242nm **Flow Rate** – 1.0ml/min **Injection Volume** - 20µl **Linearity Range**–	[27]

			TH : 0.5-16µg/ml MF : 1-32µg/ml **Regression Coefficient** – TH : 0.992 MF :0.995 **Retention Time** – TH : 2.2min MF : 3.5min **LOD** – TH : 0.631µg/ml MF : 2.10µg/ml **LOQ** – TH : 0.0378µg/ml MF : 0.126µg/ml **Tailing Factor** – TH : 0.88170 MF :1.03984	
25.	**Terbinafine HCL In Semi-Solid Dosage Form**	**HPLC**	**Column** – Inertsil:L1 ODS **Mobile Phase**–MeoH:ACN (60:40) pH7.68 **Linearity Range**– 50-150µg/ml **Regression Coefficient** – 0.9993 **Flow Rate** - 0.4ml/min **InjectionVolume** - 10µl **Detector** – PDA **Retention Time** – 4min **LOD** – 0.1µg/ml **LOQ** – 0.2µg/ml **%Recovery** – 100.43%	[28]
26.	**Terbinafine HCL In Pharmaceutical Solid Dosage Form**	**RP-HPLC**	**Column** – RP C18 **Mobile Phase**–MeoH:Water (80:20) **Detection Wavelength** - 282nm **Linearity Range** – 80-160µg/ml **Regression Coefficient** – 0.9974 **Flow Rate** – 1ml/min **Retention Time** – 5.84min **LOD** – 0.204µg/ml **LOQ** – 0.62µg/ml **%Recovery** – 99.68-100.2% **Tailing Factor** – 1.4	[29]
27.	**Terbinafine HCL In Bulk & Pharmaceutical Dosage Form**	**RP-HPLC**	**Column**– Inertsil ODS RP C18 **Mobile Phase** – Potassium dihydrogen phosphate:ACN (65:35) **Detection Wavelength** – 220nm **Linearity Range** – 50-150µg/ml **Regression Coefficient** – 0.999 **Flow Rate** – 1.5ml/min **Injection Volume** - 10µg/ml **LOD** – 0.0585µg/ml **LOQ** – 0.1950µg/ml **Tailing Factor** – 0.8 **%Recovery** – 100.193%	[30]
28.	**Terbinafine HCL In Formulated Products**	**RP-UPLC**	**Column** – Waters Acquity UPLC BEH C18 **Mobile Phase** – ACN:Water (50:50) **Detection Wavelength** – 222nm **Linearity Range** – 25-150µg/ml **Regression Coefficient** – 0.9999 **Detector** – UV **Retention Time** – 2.5min **Flow Rate** – 0.6ml/min **%Recovery** – 97.66-98.53%	[31]

29.	**Terbinafine HCL In Pharmaceutical Solid Dosage Form**	**HPTLC**	**Plate** – Aluminium backed silica gel 60 F254TLC Plate **Mobile Phase** – ACN:1,4dioxan:Hexane:Acetic Acod (1:1:8:0.1) **Detection Wavelength** – 282nm **Linearity Range** – 500-4500ng/spot **Regression Coefficient** – 0.9975 **LOD** – 298.62ng/spot **LOQ** – 385.9ng/spot **R_f Value** – 0.45 **%Recovery** – 99.79-99.74%	[32]
30.	**Terbinafine In Bulk Drug**	**HPTLC**	**Plate** – Silica Gel 60F254 **Mobile Phase** – n hexane:Acetone:GAA(8:2:0.1) **Detection Wavelength** – 223nm **Linearity Range** – 200-1000ng/spot **Regression Coefficient** – 0.9997 **LOD** – 1.204ng/spot **LOQ** – 3.648ng/spot **R_f Value** – 0.42 **%Recovery** – 100.85%	[33]
31.	**Terbinafine HCL & Mometasone Furoate In Combined Dosage Form**	**HPTLC**	**Plate –** Silica Gel Aluminium Plate 60F254 **Mobile Phase –** Toluene:EthylAcetate:GAA (8:4:0.1) **Detection Wavelength**– 248nm **Linearity**– TH : 1000-3000ng/spot MF : 100-300ng/spot **Regression Coefficient**– TH : 0.999 MF : 0.998 **LOD**– TH : 42.22ng/spot MF : 2.56ng/spot **LOQ**– TH : 127.93ng/spot MF : 7.75ng/spot **R_f Value** – TH : 0.62 MF : 0.35 **%Recovery** – TH : 100.56% MF : 99.27%	[34]

CONCLUSION

This review portray the reported Spectroscopic and Chromatographic methods developed and validated for estimation of Itraconazole and Terbinafine HCL. In the present study it was concluded that for Itraconazole and Terbinafine HCL different Spectroscopic and Chromatographic methods are available for single and combination with other drugs. The mobile phase containing Phosphate buffer, Methanol and Acetonitrile were common for most of the chromatographic method to provide more resolution with flow rate in the range 0.4 – 1.5ml/min. For most of the Spectroscopic methods common solvent is Methanol. These all methods claimed to be simple, accurate, economic, precise and reproducible in nature. Most of these methods were using RP-HPLC and UV absorbance detection.

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