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Analytical method development and validation of an allylamine antifungal drug, Terbinafine hydrochloride: A review

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Abstract:

Terbinafine hydrochloride is a BCS Class-II antifungal drug. It belongs to allylamine antifungals with low solubility and high permeability.[95] Various analytical methods are used on large scale for qualitative and quantitative estimation of various drugs. A useful method for research laboratories involved in the routine analysis of this drug will be provided with the drug as single active ingredient or with combination with other active ingredients or a comparative study of various antifungal drugs. Methods used widely in different studies such as UV, LC/MS, UPLC, HPLC, GC/MS, HPTLC, GC, Ion pair Electrophoresis, Micellar chromatography, UFLC for the qualitative and quantitative analysis of Terbinafine hydrochloride in various samples like tablets, creams, plasma, other biological samples, etc. This article summarizes such, many reported methods which have been already developed and analysed which will make the researchers an ease to study important information related to study development of Terbinafine hydrochloride as per ICH guidelines.[90]

Keywords: Terbinafine hydrochloride, stationary phase, mobile phase, UV, HPLC, LCMS, UPLC, HPTLC, GC, biological samples, etc.

Introduction:

Terbinafine hydrochloride (TBHCL) (Fig. 1) is a BCS Class-II (low solubility and high permeability), belonging to allylamine antifungal drugs. In IUPAC system it is named as [(2E)-6,6-dimethylhept-2-en-4-yn-1-yl] (methyl) (naphthalen-1-ylmethyl) amine hydrochloride with brand name Lamisil.[3] TBHCL in 1991 was first available in Europe and in 1996 in the US. It is included in the World Health Organization's List of Essential Medicines and is been largely prescribed till date. TBHCL is very slightly or slightly soluble in water, slightly soluble in acetone, freely soluble in anhydrous ethanol and in methanol.[1] Due to the highly lipophilic nature of TBHCL it may be likely to accumulate in fatty cells, tissue, skin, hair and nails.

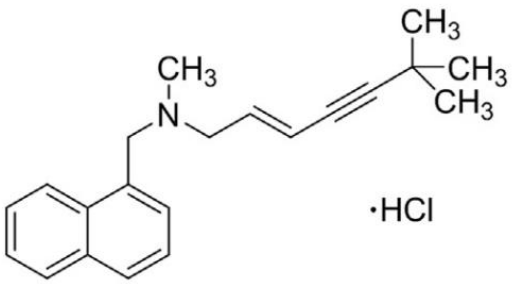


Fig. 1. Terbinafine hydrochloride.

Terbinafine, a systemic allylamine antifungal was synthetically produced by Novartis with brand name Lamisil®. When 1,3-dichloropropene is reacted with neohexene by olefin metathesis and later than by reaction with N-methyl-1-naphthalenemethanamine it produces Terbinafine. It is also reported from natural source for the first

time. It was isolated from the culture of Streptomyces species KH-F12 isolated from soil sample from Adilamm, Saudi Arabia. [87] TBHCL is persuasive on Onygenales (consume and break down keratin) of fungi group and few yeasts in the genus Candida (yeast infection or thrush). It belongs to Oral and topical antifungal age of Pharmacotherapeutic group. TBHCL is useful for Treatment in adults of ringworms such as tinea corporis, tinea cruris, tinea pedis which is caused by dermatophytes such as Trichophyton e.g., T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum; this skin infection takes several weeks for complete resolution of signs and symptoms. Also where topical therapy does not work and needs oral therapy in case of Microsporum canis and Epidermophyton floccosum. Onychomycosis in adults is also treated using TBHCL, the duration for successful treatment may take 6 weeks to 3 months. TBHCL is absorbed more than 70% when administered orally and considering the first-pass metabolism it is approximately 40% bioavailable from Lamisil tablets. A 250 mg terbinafine leads to peak plasma conc. (Cmax) of 0.83 µg /mL within 2 hrs of administration of single oral dose. TBHCL has an absorption half-life of around 1 hr with a distribution half-life of 4.6 hrs. It shows 99% plasma proteins binding and concentrates in lipophilic stratum corneum layer of the skin. [2-7]

Mechanism of Action

Ergosterol is an important constituent of fungal cell, it plays a role in fungal cell wall formation. Terbinafine hydrochloride (TBHCL) like all other allylamine drugs, inhibits the enzyme squalene monooxygenase which is also known as squalene epoxidase (present in fungal cell), thus arrest squalene to 2,3-oxydosqualene conversion, which is a step in production of ergosterol. Thus, the decrease in ergosterol synthesis will hamper the process of cell wall formation and thus alter the fungal cell growth. Also, the accumulated squalene containing vesicles in the cytoplasm of the fungal cell can ooze other lipids and important constituents, further weakening the cell wall thus leading to the death of the fungal cell, as the contents of the cell are now unprotected in absence of cell wall. Squalene epoxidase is not linked to cytochrome P450 enzyme. The metabolism of other hormones or any drugs is not influenced by TBHCl. There is accumulation of the TBHCl in the skin, nails, hairs after its oral administration which may last up to 15-20 days even after discontinuation of the treatment.[91]

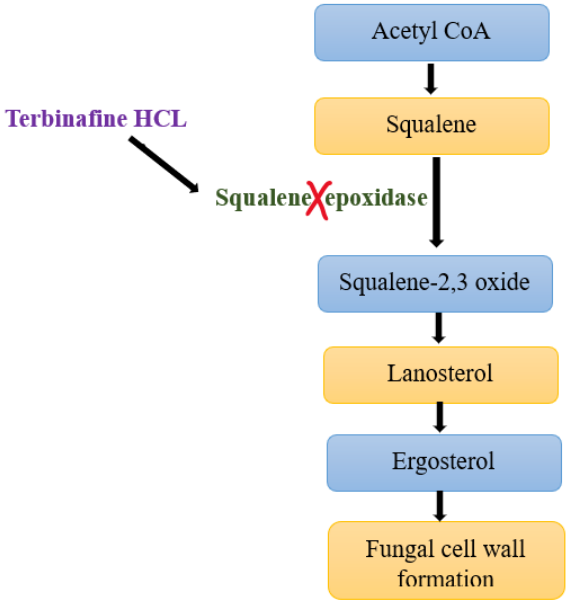


Fig 2. Mechanism of action of Terbinafine HCl

Pharmacoki l that after the first-pass metabolism

Absorption-V by the liver it is bioavailable approximately 50%. Within 1.5 hours of oral administration of 250 mg of TBHCl it shows an average peak plasma concentration of 1.3 ug/mL. Its bioavailability is very less affected by the food with no significant changes. When the approx. 70% of steady state levels of TBHCL is achieved then the peak concn. was found to be 25% more. [5]

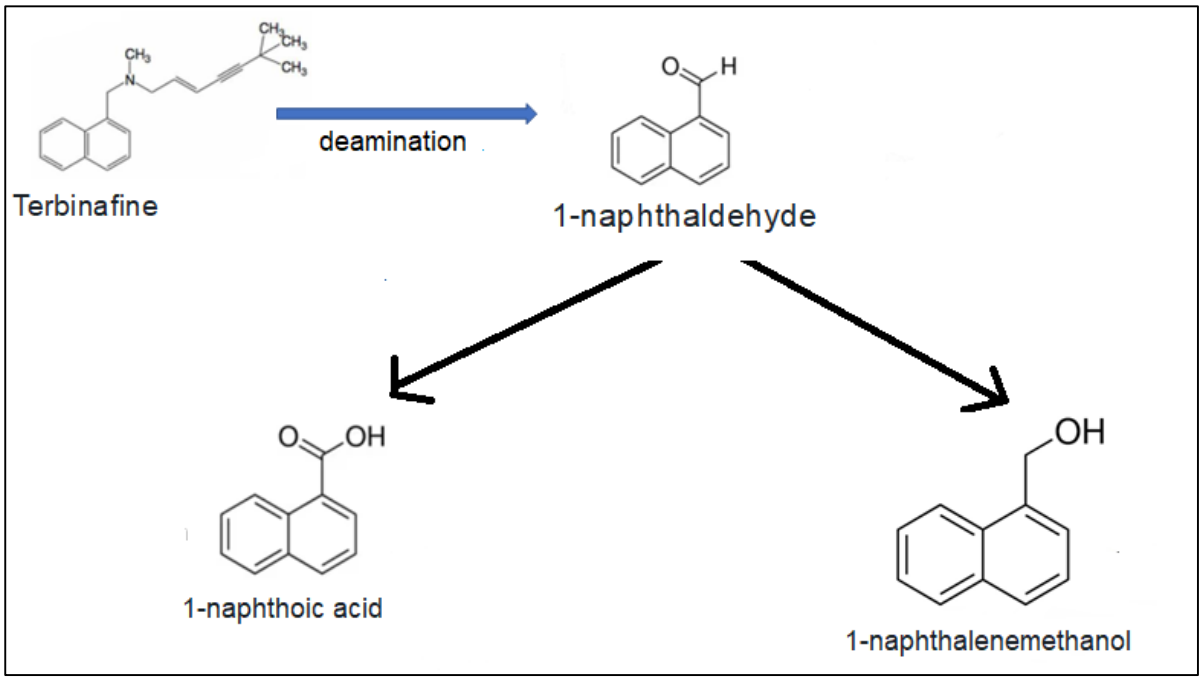
Distribution-Terbinafine shows a 99% plasma protein binding as it is concentrated in stratum corneum(lipophilic) after the quickly diffuse across the dermis. It is also secreted in sebum rich skin, hair follicles, nails, etc with a 4.6 hrs of distribution half-life.[87]

Metabolism and Excretion- The CYP-type of enzmyes are responsible for the fast metabolism of TBHCl. The seven isoenzymes mainly consist of CYP3A4, CYP2C9, CYP2C19, CYP1A2, CYP2C8, etc. After the

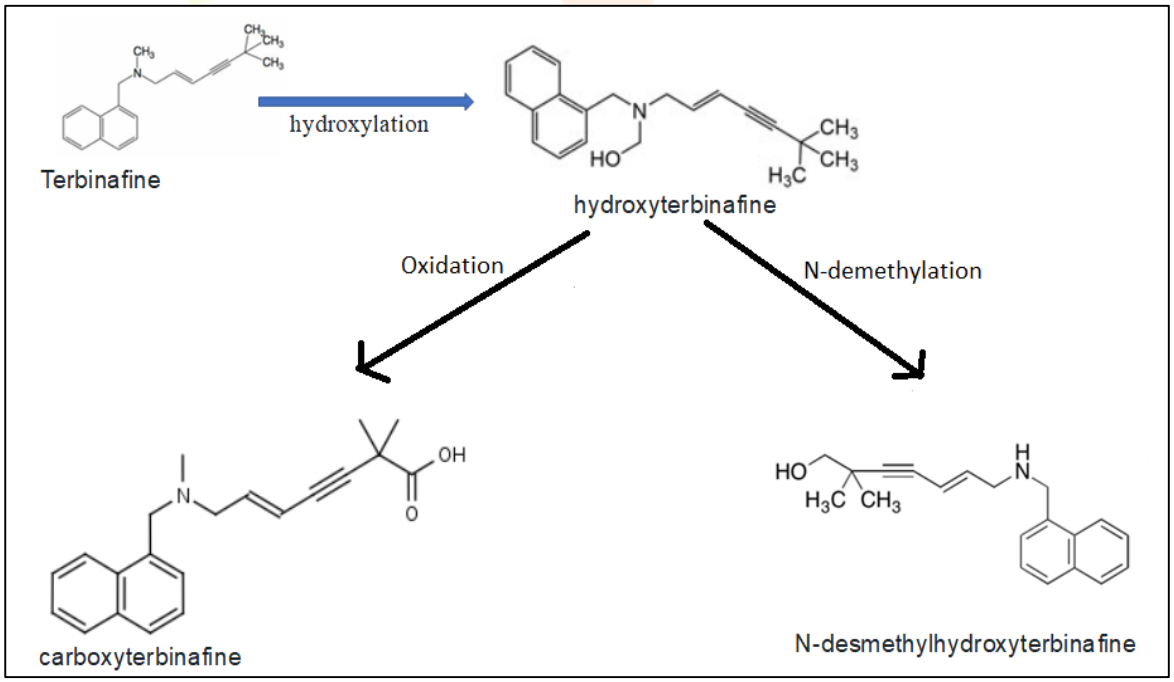
biotransformation of Terbinafine into its metabolites, they are excreted via urine with no any antifungal property.Extended blood sampling after the administration of multiple doses demonstrated a three phase elimination which has terminal half-life of almost 16.5 days.[5]

Metabolites of Terbinafine HCl[91]

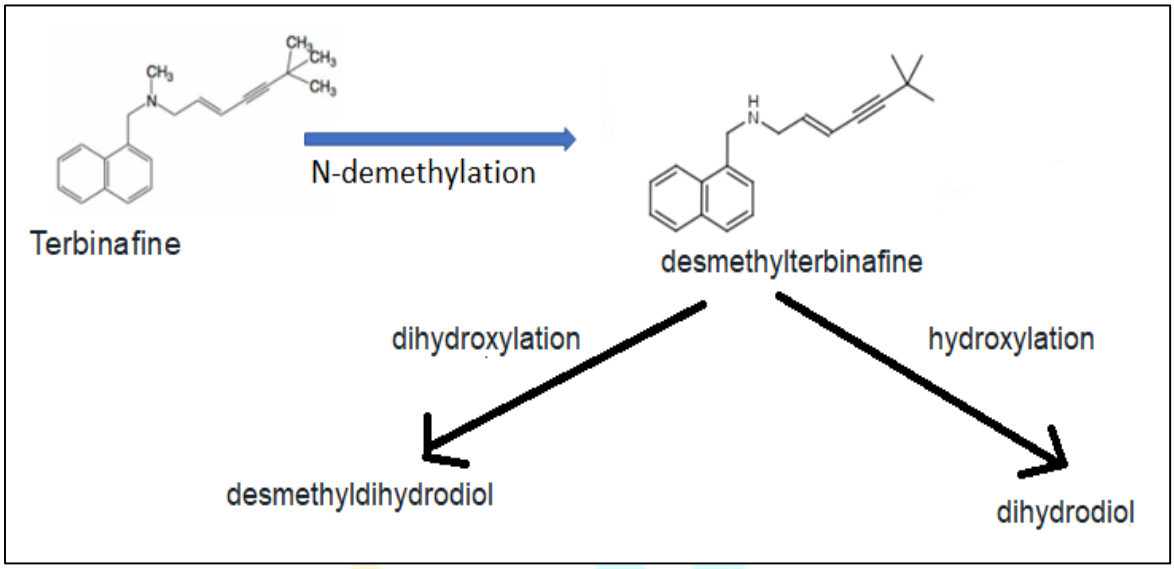
1) Deamination by CYP2C9, 2B6, 2C8, 1A2, 3A4, and 2C19.



2) Hydroxylation by CYP1A2, 2C9, 2C8, 2B6, and 2C19



3)N-demethylation by CYP3A4, 2B6, 1A2, 2C9, 2C8, and 2C19



Introduction to UV Spectroscopy and Spectrophotometry methods.

Spectroscopy Methods is a science branch which deals with the learning of interaction of Electromagnetic radiation with molecule. A broad range of samples are analysed using this powerful method which studies the atomic and molecular structures. It includes a region between 100 Å and 400 µm of the electromagnetic spectrum.[84-85]

Electromagnetic spectrum regions are as follows

Region	Wavelength
Far (or vacuum) ultraviolet	10-200 nm
Near ultraviolet	200-400 nm
Visible	400-750 nm
Near infrared	0.75- 2.2 µm
Mid infrared	2.5-50 µm
Far infrared	50-1000 µm

Ultraviolet-Visible Spectrophotometry: It is a most widely used analysis technique that involves the measurement of the UV or Visible radiation that is absorbed by the molecules in the solution; which is measured by instruments called UV-Vis Spectrophotometers. It follows the Beer-Lambert laws which states that when a beam of light is passed across a transparent cell which contains a solution of an absorbing substance then reduction of the intensity of light may occur. Mathematically, Beer-Lambert law can in given as;[83]

A = a b c

Where, A = absorbance; a = absorptivity; b = path length (cm) of cell of sample; c = concentration of solution.

For the multi component analysis of sample by spectrophotometer various methods are used as follows;

1. Simultaneous equation method

2. Derivative spectrophotometric method

3. Absorbance ratio method (Q-Absorbance method)

4. Difference spectrophotometry method

Various UV methods used for the method development and validation of Terbinafine HCL in various articles are as follows:

[11] Present work shows the UV spectrophotometric method for simultaneous estimation of Itraconazole and Terbinafine HCl in bulk and pharmaceutical tablet dosage form. For 24 hours both drug solutions were stable. UV Shimadzu 1800 model and acetonitrile was used as a solvent for the UV method development. The wavelength of 235 nm was used as λmax for TBHCL. The percent recovery of TBHCL was determined in the range of 98 – 102 % with a linear range of 5-15 ug/ml, r2 values for TBHCL was found to be 0.9995.

[12] This paper discusses about the method of development by two different UV spectroscopy methods for Terbinafine HCl, Telmisartan and Ramipril based on their bromine reactivity. Method A reaction of unreacted bromine with methylene blue in distilled water at 678 nm wavelength. The percent recovery of TBHCL was determined in the range of 99-101 % with a linear range of 1–3ug/ml, r2 values for TBHCL was found to be 0.9999. LOD was determined at 0.3ug/mL and LOQ was found to be 0.95ug/ml. Method B reaction of unreacted bromine with methyl red in distilled water at 517 nm wavelength. The percent recovery of TBHCL was determined in the range of 98-101 % with a linear range of 0.5– 2.5 ug/ml, r2 values for TBHCL was found to be 0.9995. LOD was determined at 0.15 ug /mL and LOQ was found to be 0.46 ug/ml.

[13] Objective of this method is to develop and validate the UV spectrophotometry for TBHCL in bulk and pharmaceutical formulation. Methanol was used as a solvent for the UV spectrophotometry method development. The detection wavelength of 224 nm was used for TBHCL. The percent recovery of TBHCL shown in the range of 99.58– 102.78% along with a linearity range from 0.4– 2.8ug/ml, corelation coefficient value for TBHCL was found to be 0.999. LOD was found to be 0.03µg/mL and LOQ of 0.091 µg/mL was found. Good label claim value was established with 99.58%-102.78% amount of drug found.

[14] Present work shows the Ultraviolet spectrophotometric determination of pure form of terbinafine hydrochloride (TH) and fluconazole (FLZ). Two methods distinguished by two different wavelengths. In first method 0.1N HCl solvent with a detection wavelength of 222nm was used for the UV analysis. LOD was found to be 0.067µg/mL and LOQ was found to be 0.203µg/mL. % RSD value was found within limits.The percent recovery of TBHCL was determined in the range of 98.50 %-103.96 % with a linear range of 0.5– 3.0 µg/ml, Regression coefficient value was found to be 0.999.In second method 0.1N HCl solvent with a detection wavelength of 239nm was used for the UV analysis. LOD was found to be 0.175µg/mL and LOQ was found to be 0.531µg/mL. Percent accuracy of TBHCL was determined in the range of 98.50 %-103.96 % with a linear range of 0.5– 3.0 µg/ml. Correlation coefficient value was found to be 0.999.

[15] Objective of this method is to develop and validate the UV spectrophotometry for TBHCL in bulk and tablet. Solutions were scanned in the UV range using methanol: glass distilled water in a ratio of 70:30 v/v as a solvent against blank. The wavelength of 223 nm was used as λmax for TBHCL and obeyed Beer's law. The percent recovery of TBHCL was determined at 98.46 % with a linear range 0.6– 3.8µg/ml, r2 value for TBHCL was found to be 0.9989.

[16] In this work it shows the Ultraviolet spectrophotometric determination for assay of Terbinafine HCl with Telmisartan in API and in tablet based on their oxidation with a known amount of potassium permanganate in alkaline medium. At 609 nm absorbance was measured for coloured manganate ions. Distilled water was used as a solvent for the UV method development. LOD was determined at 0.65µg/mL and LOQ was found to be 1.96µg/mL. % RSD value was found within limits and r2 value was found to be 0.9999 for TBHCL. The percent recovery of TBHCL was determined in the range of 98-101 % with a linear range of 02–16µg/ml.

[17] Terbinafine hydrochloride (TBHCL) and Mometasone furoate (MF) cream used for corticosteroid responsive dermatoses is been estimated in this work. UV spectrophotometric method is based on absorption correction method. Solutions were scanned on UV using methanol as a solvent against blank. The wavelength of 282 nm was used as λmax for TBHCL. Analysis results have been statistically validated and the linear range of 10–70µg/ml was estimated. The percent recovery of TBHCL was determined in the range of 100 – 102 % and correlation coefficient value for TBHCL was found to be 0.999. LOD was determined at 0.5µg/mL and LOQ was found to be 1.67 µg/mL. % RSD value was found within limits.

[18] This paper discusses about the method of development and validation by UV spectroscopy for TBHCL pure form and its tablet formulation. Solutions were scanned in the UV range using methanol as a solvent against blank. The wavelength of 282 nm was used as λmax for TBHCL and obeyed Beer's law. The percent accuracy of TBHCL was determined at 99.82-100.2 with a linear range 8–24µg/ml, Linearity coefficient (r2) value for TBHCL was found to be 0.998. LOD was determined at 0.35µg/mL and LOQ was found to be 0.81µg/mL.

[19] UV-spectrophotometric method using inorganic solvents like hydrochloric acid, sodium hydroxide for the analysis of TBHCL in bulk and tablet can be developed. Solutions were scanned in the UV range using 0.1N HCl was used as inorganic solvent for the UV method development against blank. The wavelength of 223 nm was used as λmax for TBHCL which obeyed Beer-Lambert's law. The percent recovery by standard addition method of TBHCL was determined in the range of 99.16 -100.75 % with a linear range of 1-3.5µg/ml, correlation coefficient value for TBHCL was found to be 0.995 . LOD was determined at 0.086µg/mL and LOQ was found to be 0.26µg/mL. Corresponding molar absorptivity value was found within limits.

[20] Present work shows the Ultraviolet spectrophotometric determination of by two ways for the assay of TBHCL, Telmisartan and Ramipril in bulk drugs and its dosage forms. Direct spectrophotometric method (A), include ceric (IV) sulphate (in distilled water) addition to drug in acidic medium at detection wavelength of 319 nm against blank reagent. LOD was determined at 1.06µg/mL and LOQ was found to be 3.53µg/mL. The percent recovery was found in the range of 98 – 101 % with a linearity range of 1–9µg/ml and r2 value was found to be 0.9999 for TBHCL. Indirect spectrophotometric method (B), include ceric (IV) sulphate (in distilled water) addition to drug in acidic medium, then reacting fixed amount of chromatrope 2R with unreacted ceric at detection wavelength of 507 nm against blank reagent. LOD was determined at 0.93µg/mL and LOQ was found to be 3.11µg/mL. The percent recovery was found in the range of 98 – 102 % with a linearity range of 1–7µg/ml and r2 value was found to be 0.9997 for TBHCL .

[21] Present work shows the Ultraviolet spectrophotometric determination of TBHCL in bulk and formulation. Solutions were scanned in the U. V. range using distilled water as a solvent for the UV method development against blank. The wavelength of 283 nm was used as λmax for TBHCL and obeyed Beer's law. The percent recovery by standard addition method at 80%, 100%, and 120% of TBHCL was determined in the range of 98.54–99.98 % with a linear range of 5–30 µg/ml, r2 value for TBHCL was found to be 0.999. LOD was determined at 0.42µg/mL and LOQ was found to be 1.3µg/mL. The % amount of drug estimated was 99.19 and the % RSD value less than 2 shows precise method.

[22] Objective of this method is to develop and validate the UV spectrophotometry for TBHCL in bulk and tablet formulation. 0.1 mol/L HCl was used as a solvent system for the UV spectrophotometry method development. The detection wavelength of 223 nm was used for TBHCL. The percent recovery of TBHCL shown in the good range along with a linearity range from 1–3.5ug/ml, corelation coefficient value for TBHCL was found to be 0.99. LOD was found to be 0.086µg/mL and LOQ of 0.26µg/mL was found. Good label claim value was established.

[23] Objective of this method is to develop and validate the UV spectrophotometry by formation of coloured ion-association complex of terbinafine hydrochloride TBHCL and clarithromycin CAM and picric acid. Series of solution (keeping one parameter fix and other variable such as ratio of mobile phase, extracting solvent, temperature, time, etc.) were scanned in the U. V. range at lambda max of 350 nm using 0.1 N HCl: double distilled water in a ratio of 5:95 as a solvent for the UV method development against blank. The percent recovery by standard addition method of TBHCL was determined in the range of 98 – 100 % with a linear range of 2.5-15 µg/ml, r2 value for TBHCL was found to be 0.9999 . LOD was determined at 0.1299µg/mL.

[24] This paper discuses about the 3 different methods of development by UV spectroscopy for Luliconazole and TBHCL combination and their comparison by ANOVA. In Method A, first order derivative spectrophotometric technique is involved where the detection wavelength for TBHCL is 258.50 nm. Methanol was used as a solvent for the UV method development. The linearity range was observed within 3–18µg/ml, Coefficient of correlation value for TBHCL was found to be 0.9991. LOD was determined at 0.0138µg/mL and LOQ was found to be 0.042µg/mL. In Method B, dual wavelength method where the absorbance difference at 262 and 296 nm for TBHCL is considered. Methanol was used as a solvent for the UV method development. The linearity range was observed within 3–18µg/ml, Coefficient of correlation value for TBHCL was found to be 0.9996. LOD was determined at 0.469µg/mL and LOQ was found to be 1.421µg/mL. In Method C, Q-absorbance ratio method

where at 282 nm iso-absorptive point was obtained is used for the analysis. Methanol was used as a solvent for the UV method development. The linearity range was observed within 3–18µg/ml, Coefficient of correlation value for TBHCL was found to be 0.9997. LOD was determined at 0.066µg/mL and LOQ was found to be 0.2µg/mL.

[25] Present work shows the Ultraviolet spectrophotometric determination of by first spectral derivation (1D) and also first derivative of the ratio spectra (1DD) of the TBHCL drug and its photodegraded products at different wavelengths. Solutions were scanned in the U. V. range using a solvent against blank. The linearity range of 10-100 µg/ml was determined, r2 value for TBHCL was found to be 0.99. LOD was determined as > or = 1.11µg/mL and LOQ was found to be > or = 3.36µg/mL. % RSD value was found within limits.

[26] This paper discuses about TBHCL and triamcinolone acetonide estimation by two different UV spectrophotometry methods. First derivative spectrophotometric method was used in method A at two different lambda max of, at 297nm, concentration ranges were of 5-30µg/ml with percent accuracy of 99.90+/-0.67 and at 274nm, concentration ranges were of 4-24µg/ml with percent accuracy of 100.25+/-0.49. Ratio-spectra 1st derivative spectrophotometry method was used as method B at two different lambda max of, at 298nm, with percent accuracy of 100.22+/-0.51 and at 248nm, with percent accuracy of 99.93+/-0.56.

[27] It briefs the method of development by ultraviolet spectrophotometric and a nonaqueous volumetric in TBHCL in raw materials, tablets, and creams. The maximum detection wavelength of TBHCL in water was found to be 224nm. Methanol was used as a solvent for the UV method development against blank. The percent recovery of TBHCL was determined as 99.9 % for tablet 102 % for cream along with a linearity range of 0.8-2.8µg/ml, r2 value for TBHCL was found to be 0.9997. Precision was found to be 101.3%, CV = 0.96%, for creams and for tablets it was found to be 100.25%, CV = 1.08% [n = 9 for both].

[28] The proposed methods were applied for determination of TBHCL in tablets by stability indicating (acid, base, thermal, photolytic, etc) two UV-spectrophotometric methods. In method A, 0.1 mol/L HCl solvent with a detection wavelength of 222nm was used for the UV analysis. LOD was found to be 0.003µg/mL and LOQ was found to be 0.01µg/mL. The corresponding molar absorptivity value of 8.7 x 104 L mol-1 cm-1 was observed. The linear range of 0.2–4.0µg/ml was found and Corelation coefficient value was found to be 0.9999. In method B, 0.1 mol/L acetic acid solvent with a detection wavelength of 28 2nm was used for the UV analysis. LOD was found to be 0.09µg/mL and LOQ was found to be 0.27µg/mL. The corresponding molar absorptivity value of 7.9 x 103 L mol-1 cm-1 was observed. The linear range of 2.0–50µg/ml was found and Corelation coefficient value was found to be 0.9997. In both methods substantial oxidative degradation and no degradation with other stress conditions was observed.

Sr. No	Solvent	Detection Wavelength	LOD (ug/mL)	LOQ (µg/mL)	% Recovery range	Linear range (µg/mL)	r2 value	Application	Ref No
1	Acetonitrile	235	–	–	98 – 102 %	5 –15	0.9995	bulk, tablet	11
2 (a)	distilled water (Methylene blue)	678	0.3	0.95	99-101 %	1–3	0.9999	bulk, tablet	12
2(b)	distilled water (Methyl Red)	517	0.15	0.46	98-101 %	0.5– 2.5	0.9995	bulk drug and tablet	12
3	methanol	224	0.03	0.091	99.58– 102.78%	0.4– 2.8	0.999	bulk, formulation	13
4(a)	0.1N HCl	222	0.067	0.203	98.50 %- 103.96 %	0.5– 3.0	0.999	bulk drug	14
4(b)	0.1N HCl	239	0.175	0.531	98.50 %- 103.96 %	0.5– 3.0	0.999	bulk drug	14
5	methanol: glass distilled water (70:30)	223	–	–	98.46	0.6– 3.8	0.9989	bulk, tablet	15
6	distilled water	609	0.65	1.96	98-101 %	02–16	0.9999	bulk, tablet	16

7	methanol	282	0.5	1.67	100 – 102 %	10–70	0.999	bulk, Cream	17
8	methanol	282	0.35	0.81	99.82-100.2	8–24	0.998	bulk, tablet	18
9	0.1N HCl	223	0.086	0.26	99.16 - 100.75	1-3.5	0.995	bulk, tablet	19
10(a)	distilled water[Cerium(IV) sulphate]	319	1.06	3.53	98-101 %	1–9	0.9999	bulk, tablet	20
10(b)	distilled water [Cerium(IV) sulphate + C2R]	507	0.93	3.11	99-102 %	1–7	0.9997	bulk, tablet	20
11	distilled water	283	0.42	1.3	98.54–99.98	5–30	0.999	bulk, tablet	21
12	0.1 mol/L HCl	223	0.086	0.26	–	1–3.5	–	Tablets	22
13	0.1 N HCl: double distilled water (5:95)	350	0.1299	–	98-100 %	2.5-15	0.9999	Tablets, creams	23
14(a)	methanol	258.5	0.0138	0.042	–	3–18	0.9991	bulk, Cream	24
14(b)	methanol	262 & 296	0.469	1.421	–	3–18	0.9996	bulk, Cream	24
14(c)	methanol	282	0.066	0.2	–	3–18	0.9997	bulk, Cream	24
15	–		1.11	3.36	–	10–100	–	with degradation products	25
16	–	297; 298	–	–	–	5–30 ; 4-24	–	Tablets, creams	26
17	methanol	224	–	–	99.9 % for tablet 102 % for cream	0.8-2.8	0.9997	bulk, tablet, cream	27
18(a)	0.1 mol/L HCl	222	0.003	0.01	–	0.2–4.0	0.9999	Bulk, tablets	28
18(b)	0.1 mol/L acetic acid	282	0.09	0.27	–	2.0–50	0.9997	Bulk drug, tablets	28

Introduction to HPLC and UPLC method

[86] In 1903, chromatography was first developed by a Russian Botanist M.S. Tswett which is now been used as a modified version High-performance liquid chromatography (HPLC) for analysis of more than 80% of the compounds. HPLC consist of stationary phase and mobile phase having opposite polarity for the separation of various components and its identification and quantification. For the development of the method various literature surveys and trials need to be done for the selection of appropriate mobile phase, stationary phase, buffer, UV wavelength, column temperature etc. [89] The method developed should be economic, easy, considerable etc. Considering all these parameters then the method is optimized for the final results.[1] Validation of method is done further by the optimised system. Method validation provides documented evidence that method performs with the acceptable parameters and is bias and precise. [88]Different Types of Validation characteristics are precision, accuracy, specificity, linearity, range, detection limit, quantitation limit, ruggedness, robustness. As per ICH guidelines system suitability is "checking of the system, previously or while performing the analysis of unknown samples, to ensure system performance." It includes factors like retention, tailing, plate count, %RSD, capacity, resolution, etc. [7]

Sr. No.	Parameter	Acceptance criteria
1	Number of theoretical plates or Efficiency (N)	> 2000
2	Relative Standard Deviation (RSD)	< 2
3	Resolution (Rs)	> 1.5
4	Tailing factor or Asymmetry(T)	< 2
5	Separation or Relative retention (α)	> 1
6	Capacity factor (K)	< 1

[86]

UPLC is an advance method of liquid chromatograph which is referred as Ultra Performance Liquid Chromatography. Though the method uses the same principle as the HPLC but is much more powerful than HPLC as it brings dramatic improvements in the speed of analysis with a good resolution and sensitivity as a very high pressure above 6000 psi. Also due to the use of small particles (< 2.5µm) and shorter columns the time required for elution is also reduced and less use of solvents is observed. [57-60]

Various HPLC and UPLC methods used for the method development and validation of Terbinafine HCL in various articles are as follows:

[29] To accomplish simultaneous determination of TBHCl and mometasone furoate in cream dosage form, the method uses column C18 as a stationary phase and water: methanol (5:95v/v) as mobile phase at a flow rate of 1.2 mL/min. UV detection at 248 nm was estimated. The linearity was estimated in the range of 20-200µg/mL for TBHCl, with retention time of 6.9 min. A precise and accurate RP-HPLC method with LOD value 5.57µg/mL and LOQ value 16.87µg/mL; with the % recovery of 101.18%.

[30] Chromatography was carried out for the determination of TBHCl in hydroalcoholic solutions and tablets, used for dissolution test on an using a RP-C18 (250 mm × 4.6 mm, 5 µm) Vertical column. Mobile phase consists of methanol and water in the ratio of 95:5, v/v, detected on UV-Vis at 254 nm, at a flowrate of 1.2 mL/min. Method validation parameters like the linearity was found to be in the range of 20-200µg/mL. The LOD value was found to be 0.9µg/mL and LOQ value was found to be 2.7µg/mL. Retention time for TBHCl was determined of 6 min. Other parameters like precision, robustness and specificity, were within the acceptable limits. Dissolution of 80% of tablet was achieved faster within 15 min.

[31] TBHCl was determined with an ion-pair reversed phase liquid chromatographic method (IP-RP-HPLC) in bulk and tablet dosage form. A C18 column was employed as stationary phase along with the mobile phase which includes of sodium 1-heptanesulfonate (0.2%) an aqueous acid solution (adjusted with ortho-phosphoric acid, pH 2.0), as ion-pairing reagent, and acetonitrile (ACN) in a ratio of 60/40 v/v. Linearity of the method was estimated at a range of 10 –60µg/mL and the retention time was determined at 7.08 minutes. The absorption maxima was selected as 220 nm. The method was reproducible with detection limit of 1.21µg/mL and quantification limit of 3.67 µg/mL.

[32] HPLC method which is sensitive and rapid for the assay of TBHCl in tablet dosage forms was optimised and developed. TBHCl was chromatographed on a RP-C18 column as a stationary phase and buffer and acetonitrile containing mobile phase in the ratio of 65:35 v/v. The elution was carried out at 220 nm with a mobile phase pumped at the rate of 1.8 mL/min. The method was linear in the range of 0.2-10 µg/mL for its calibration curve. The retention time for TBHCl was estimated at 14.95 min with less than 2 % values of intra- and inter-day precision. The mean recovery of the drug was determined as 99.1 ± 0.73 % from the solution containing 20 ng/mL which tells that method is highly accurate.

[33] Reversed phase chromatography was carried out on an ODS column as stationary phase and phosphate buffer and ACN 60% and 40% respectively as the chosen mobile phase. TBHCl was determined in tablet formulation at a detection wavelength of 283 nm and the flow rate of mobile phase was 1ml/min. The method showed a good linear fit in the concn. range of 0.5-50 µg/mL and the retention time of the drug was estimated to be 7.106 min. The method simple and reliable too.

[34] The method was statistically validated for its linear range, LOD, specificity, LOQ, robustness etc. and was developed using a phenomenex C18 column (250 mm 4.6 mm, 5 mm) at the lambda max chosen as 282 nm. The mobile phase was run with a flow rate of 1ml/min which consisted of water, methanol and acetonitrile in the ratio of 50:40:10, v/v/v for the assay of TBHCl in cream formulation.

[35] A compound ointment of TBHCl along with chlorhexidine and triamcinolone acetonide acetate was used to develop and validate a reversed phase HPLC method. The method employed the use of Kramosil C18, 5 mm column as the stationary phase and 0.3% sodium heptane sulphonate in methanol of pH 3.2 (adjusted with glacial acetic acid) and distilled water in the ratio of 73:27, v/v as the mobile phase with flow rate of 1ml/min and the UV absorption maxima at 248 nm. The method was accurate besides only sensitive and specific.

[36] To perform simultaneous analysis of TBHCl and bezafibrate in pharmaceutical formulation a simple, sensitive and accurate RP-HPLC method was developed. C18 column was used for the determination of the two drugs using a mobile phase adjusted to a flow rate of 1ml/min. Mobile phases composed of ratio of 15:25:60 v/v/v for water, ammonium dihydrogen phosphate and methanol, respectively. The UV detection maxima was considered at 225 nm for TBHCl with a linearity range of 2–12 µg/mL and the percent recovery was found to be 99.51%. The proposed method is statistically validated for limit of detection (LOD) value 0.05 µg/mL and limit of quantification (LOQ) value 0.15 µg/mL as per the guidelines with a retention time for TBHCl of 5.1 minutes.

[37] TBHCl along with its photo-degradation products was estimated by a quick and precise method which helped in separation and quantification of TBHCl along with triamcinolone in a dosage form. The assay was carried out by UV evaluation at 284 nm using RP-µ- Bondapak C18 column and water-methanol in ratio of 20:80 v/v as the mobile phase which was operated at the flow rate of 1.2 ml/min. The results of the proposed method were in excellently accordance with the reference method.

[38] Antimicrobial activity of terbinafine HCl was taken into consideration while optimising this microbiological assay on a cylinder culture plate of the strain of Aspergillus flavus ATCC 15546 which was used as the test microbe. This in vitro assay was completed with the help of HPLC system which uses Shim-pack CLC-ODS as the column and water-methanol in proportion of 5:95 v/v with flow rate of 1ml/min. The UV detection wavelength of 254nm was used and the method showed a linear range from 10–20 microg/ml. The precision for intra-day was CV=0.48% for tablets and 0.43% for creams. Various TBHCl creams and tablets were employed in this method.

[39] For the determination of terbinafine hydrochloride (TBHCl) in pharmaceuticals formulations a new stability indicating HPLC method was established which employed the use of Eclips XDB C-18 (3.5, 4.6, 150 mm) column with a 30ºC temperature and a mobile phase methanol, buffer 2 mL triethylamine in 1000 ml water (pH 3.4 adjusted with trifluoroacetic acid.) and isopropyl alcohol in the ratio of 48:40:12, v/v/v with a flow rate of 1mL min-1. The method was developed and validated for various parameters at lambda max of 222 nm which showed good linearity in the range of 1 - 80µg mL-1 concentration. The limits of detection (LOD) was obtained at 0.3 mg mL-1 and limit of quantification (LOQ) was obtained at 1.0 mg mL-1 . With no any interference from tablets excipients, the method which employed acid, base, photolytic, thermal, etc. showed good agreement with reference method.

[40] Chromatography was carried out on C18 column for the determination of TBHCl in semi solid formulations and optimize a method. The development used methanol and acetonitrile in proportion 60:40 v/v with (0,15% triethylamine and 0,15% phosphoric acid) as a mobile phase. The elution was carried out at 224 nm suing the UV photo diode array detector with a rate of flow of mobile phase of 0.4 to 0.6ml/min. The method validated for linear range with 5–50µg/mL, limit of detection value 0.1µg/mL, limit of quantification value 0.2µg/mL and retention time was from 5-8 min for the elution of all compounds.

[41] Reversed phase chromatography method for the quantitative estimation of TBHCl in bulk and formulations with the use of C18 column, and used potassium dihydrogen phosphate and ACN with a ratio of 65:35 v/v with flow rate set at 1.5 ml/min. Using the PDA detection at 220 nm the analysis was done. The method showed the linear range of calibration 50-150 µg/ml, with the correlation coefficient of 0.999. The limit of detection was found to be 0.058µg/mL, limit of quantification value 0.195µg/mL and retention time estimated was 6.2 min.

[42] To achieve simultaneous assay of itraconazole and TBHCl in bulk and tablet formulation a stability indicating RP-HPLC method was developed and validated. Shimadzu LC Prominence-i 2030 model was used for the lambda

max determination which was found to be 225 nm on Lab Solution software. HPLC analysis employed Shim-pack C18 GIST (250 mm×50 mm, 5 µm) column for run time of 12 min. The mobile phase made up of acetonitrile: 0.1% triethylamine (90:10 v/v) was injection with 10 µl, flow rate adjusted to 1.2 ml/min. The stability-indicating method subjected to various condition showed good linear fit at 50-150µg/mL and r2 value for TBHCl was 0.9995, the retention time displayed was 8.705 min.

[43] An eco-friendly stability indicating RP-HPLC method for determination of Itraconazole and TBHCl in bulk and tablet dosage form was studied. The method employs Shimadzu LC-20A instrument for the absorption maxima detection at 257nm. The mobile phase of methanol and water (95:5) with flow rate of 1ml/min was isocratically eluted on Zodiac C18 column (250mm x 4.6mm, 5µm). TBHCL tablet degradation products under various stress condition showed retention time of 2.551min. The method displays the good linear relation at a range of 10-50µg/mL with the Limit of Detection of 8.00µg/mL and the Limit of Quantification of 24.00µg/mL.

[44] An eco-friendly stability indicating RP-HPLC method for determination of TBHCl and Itraconazole in combined tablet dosage form was developed and validated. The method shows absorption maxima detection at 250nm. Kromasil C18 column is used as stationary phase and the mobile phase of 0.01M potassium dihydrogen orthophosphate buffer (pH 4): acetonitrile (50:50 v/v) with flow rate of 1ml/min was used for elution. TBHCL in the tablet along with its degradation products under various stress condition gave retention time of 2.289 minutes. The method shows the linear fit relation across the range of 62.5–375µg/mL with the LOD of 0.95µg/mL and the LOQ of 0.24µg/mL.

[45] Terbinafine along with clobetasol, ofloxacin and ornidazole in a cream with 2 preservatives viz; methyl and propyl paraben are quantified using HPLC and UV detection method at 243nm. And the in vitro permeation study was done on diffusion cell. The chromatographic estimation was done by using a Kinetex C8 column and 0.2% HAS(ion-pairing reagent), pH 2.7 + acetonitrile as mobile phase set for gradient elution with Flow rate 0.8 mL/min and run time of 21.02 min. The method shows the linear relation across the range of 50 -180µg/mL with the LOD of 0.11µg/mL and the LOQ of 0.34µg/mL No buffer salts were used and thus was useful for system and column life. The 3 gradient programs utilised 30% ACN for first 5 min then 60% ACN for next 7 min and again 30% ACN for 11 min.

[46] Fluconazole (FLU), itraconazole (ITR) and terbinafine (TBHCl) using a sensitive A23 full factorial design model were determined with the RP HPLC and UV detection at 210nm. MOS-1 Hypersil C18 column was used as the stationary phase and methanol and phosphate buffer (0.001% triethylamine, pH 7) in the ratio of 95:5 set in an isocratic elution with a flow rate of 0.7 ml/min as mobile phase. The method validated for linear range with 1.0–50.0µg/mL, limit of detection value 0.2µg/mL, limit of quantification value 0.6µg/mL and retention time was from 6.07 min for TBHCl.

[47] A stability indicating RP-HPLC was developed and validated for assay of TBHCL along with Ofloxacin (OFL) ,Ornidazole (ORD), clobetasol propionate(CLP) and Methyl paraben(MP) ,propyl paraben(PP) in cream. Chromatography was carried out on Zodiac C18 (250mm x 4.6mm, 5µm) column for the determination of TBHCl in semi solid formulations and optimize a method. The development used Ortho phosphoric acid buffer, PH 2.5 and Acetonitrile in proportion 82:18v/v as a mobile phase. The elution was carried out at 255 nm, with a rate of flow of mobile phase of 1ml/min. The method validated for linear range with 29 -348µg/mL, limit of detection value 0.00437µg/mL, limit of quantification value 0.001326µg/mL and retention time was from 7.302min for terbinafine.

[48] Terbinafine along with Itraconazole in bulk and tablet dosage form was simultaneous estimated using a phenomenex C18 column (150 x 4.6mm, 5.0µm) maintained at 30°C and mobile phase containing Buffer 0.1% OPA with methanol in proportion of 60:40v/v was pumped into the column at a flow rate of 1.0ml/min. The UV optimized wavelength 245 nm was selected and the linear range across the concentration of 31.25-187.5µg/mL, limit of detection value 0.94µg/mL, limit of quantification value 2.86µg/mL and retention time was 2.331 min. %Recovery was obtained as 99.95% for TBHCl and regression equation of Terbinafine was found to be y = 6951x + 2494. The method shows a decrease in the retention times and run time for the drug elution.

[49] The method involves estimation of Terbinafine and N-demethyl terbinafine (metabolite) administered in rat by HPLC after extraction of TBHCl by liquid–liquid extraction using NaOH from rat tissues. Using a RP

C18 column and a mobile phase of water and ACN in ratio of 60:40 containing ortho phosphoric acid (0.02 M) and triethylamine (0.01 M) for Ph adjustment was assayed. Clotrimazole was used as an internal standard for assay. At a lambda max of 224 nm the method showed a linear range over the concn. of 100–3000 ng/g in skin and range of 10–600 ng/g in all other tissues. For both terbinafine and its metabolite the interday as well as intraday precision was found between 0.2% and 16%. The LOQ was found to be 10 ng/g in all tissues and for skin was 100 ng/g.

[50] A single method for estimation of TBHCl, its related impurities and Chlorocresol preservatives in a topical formulation was developed using a stability-indicating RP-HPLC method. This method was formulated using a Thermo Scientific HPLC Ultimate 3000 which uses a BDS Hypersil C18 column (4.6 × 250 mm I.D., 5 µm) set at 30°C and a mobile phase consisting of buffer, methanol and ACN set in gradient elution with a flow rate adjusted to 0.8 ml/min. The retention times for Terbinafine was found to be 27.2 min with the detection wavelength of 280 nm and the linearity range over the concentration of 50-150µg/mL.

[51] Terbinafine was extracted from parrot plasma using hexane and also saline and was further evaluated using the reversed-phase HPLC which employs a Symmetry Shield RP18 (5 mm 4.6 mm 100 mm) column as stationary phase along with ACN and mixture of water, phosphoric acid, triethylamine (pH 3.0) in ratio of 35:65 as mobile phase adjusted at flow rate of 1.1 mL/min. Ultraviolet detection was quantified at 224 nm. The calibration curve ranged from the concentration of 5 to 1500 ng/mL for parrot plasma and that for the 0.9% saline was 1 to 25 mg/ml. The average recovery was more than 90%. Same LOQ values of 0.005 µg/mL was found for plasma and saline. The Limit of detection for plasma was found to be 0.005 µg/mL and for saline was 0.0025µg/mL. Both showed the retention time of 6.3 minutes for their elution This method can be used for pharmacokinetic studies in same animals and also to determine TBHCl in salt water aquariums.

[52] Present study aims to develop and validate a stability indicating reversed-phase HPLC method for assay of TBHCl in bulk and in tablet. Using a mobile phase at flow rate of 1.2 ml/min consisting of methanol: 0.5% Triethanolamine. 0.5% Triethanolamine on a Neosphere C18 (250 x 4.6 mm, 5µm) column TBHCl was determined at 250nm detection wavelength. Coefficient of corelation R2 was equal to 0.997 across the concentration range of 2-12 µg/mL. The method can be used to study the degradation products and the validation showed the LOD and LOQ values of 0.22 µg/mL and 0.66µg/mL, respectively. The retention time estimated was 4.13 minutes.

[53] Itraconazole and Terbinafine Hydrochloride in presence of their degradation products were analysed with a stability indicating HPLC method which was developed using a YMC, C18 column (150 x 4.6mm, 5µm) column and Acetonitrile: Buffer 0.1 TEA% (adjusted pH: 10) in ratio of 80:20 v/v as mobile phase with flow rate of 1ml/min. The correlation coefficient for TBHCl was found to be 0.999 with a linear range of concentration 30-80 µg/mL and percent recovery in the range of 98.28 to 101.52 %. The retention time was estimated at 15.38min with LOQ value of 4.79 µg/mL and LOQ value of 1.57 µg/mL. The percent degradation of TBHCl in acid was 7.95%, in base was 10.1% and under Oxidative stress was 2.3% along with 29.1 in thermal degradation and in Photolytic stress degradation was 5.0%.

[54] Terbinafine along with Itraconazole in bulk and tablet dosage was simultaneously evaluated by RP HPLC using a Phenomenex C18 column maintained at 30°C as stationary phase and ACN and Buffer 0.01N KH2PO4 in ratio 35 and 65 adjusted at a flow rate of 1.0 ml/min and the UV detection wavelength was 270nm. %RSD of the Terbinafine found to be 0.8 with the detection limit of 0.78 µg /mL and quantification limit of 2.37 µg /mL. The %Recovery was obtained as 100.36% along with regression equation of Terbinafine y =21293x + 9314.3 which shows the linearity over the range of 31.25-187.5 µg /mL. The retention time was noted as 2.221 min. The method adopted showed a decrease in run time and also in retention time making the method economical.

[55] A newer RP-HPLC method was developed and validated for the estimation of terbinafine hydrochloride and mometasone furoate in pharmaceutical formulations such as tablets and creams. Enable C18 column was used as stationary phase along with 33:67 v/v ratio of 0.1% Orthophosphoric Acid pH 3 and Acetonitrile as mobile phase employed at a flow rate of 1.0ml/min. The UV detection was carried out at 242nm.The method showed good linear range with 0.5-16µg/ml with limit of detection value 0.631µg /mL, limit of quantification value 0.0378 µg /mL and retention time was 2.2 min. % Recovery was found in the range of 99.98-100.07%.

[56] Chromatography was carried out on RP C18 column for the determination of TBHCl in pharmaceutical formulations and to optimize a method. The development used methanol and water in proportion 80:20 v/v with as a mobile phase. The elution was carried out at 282 nm using the UV PDA detection with a rate of flow of mobile phase of 1ml/min. The method validated for linear range with 80-160µg/ml, limit of detection value 0.204µg /mL, limit of quantification value 0.62µg /mL and retention time was 5.84 min with tailing factor 1.4. The regression coefficient was found to be 0.9974 with %Recovery of 99.68-100.2% for TBHCl.

Sr. No.	Column	Mobile phase (MP)	Proportion of MP	Detection Wavelength (nm)	Flow rate(ml/min)	LOD (µg/mL)	LOQ (µg/mL)	Linear range (µg/mL)	Retention time(min)	Application	Ref no.
1	column C18	methanol and water	95:5 v/v	248	1.2	5.57	16.87	20-200	6.98	bulk, Cream	29
2	RP-C18	methanol and water	95:5 v/v	254	1.2	0.9	2.7	20-200	6	bulk, hydroalcoholic solutions and tablets	30
3	C18 column	sodium-1-heptane sulphonate (adjusted with H3PO4) and acetonitrile	60:40 v/v	220	1	1.21	3.67	10 –60	7.08	bulk, tablet	31
4	Bondapak C18 column	buffer-acetonitrile	65:35 v/v	220	1.8	–	–	20–1000	14.95	bulk, tablet	32
5	ODS column	phosphate buffer and acetonitrile	60:40 v/v	283	1	–	–	0.5–50	7.106	Tablets	33
6	phenomenex C18 column	water–acetonitrile–methanol	50:40:10 v/v/v	282	1	–	–	–	–	cream	34
7	Kramosil C18	0.3% sodium heptane sulphonate in methanol of pH3.2 (adjusted with glacial acetic acid)-distilled water	73:27 v/v	248	1	–	–	–	–	ointment	35

8	C18 column	water–ammonium dihydrogen phosphate–methanol	15:25:60 v/v/v	225	1	0.05	0.15	2–12	5.1	dosage form	36
9	RP-µ-Bondapak C18 column	water-methanol	20:80 v/v	284	1.2	–	–	–	–	photo degradation products	37
10	Shim-pack CLC-ODS	water-methanol	5:95 v/v	254	1	–	–	10–20	–	tablets and creams	38
11	Zorbax Eclips XDB C-18	buffer (1000 mL water, 2 mL triethylamine, pH 3.4 adjusted with trifluoroacetic acid.), isopropyl alcohol and methanol	40:12:48 v/v/v	222	1	0.3	1	1–80	–	tablets	39
12	Intersil C18 column	methanol and acetonitrile	60:40 v/v	224	0.4 to 0.6	0.1	0.2	5–50	5-8 min	Semi-solid dosage forms, cream	40
13	C18 column	Potassium dihydrogen phosphate and Acetonitrile	65:35 v/v	220	1.5	0.058	0.195	50-150	6.2	bulk, tablet	41
14	Shim-pack C18 GIST	acetonitrile and 0.1% triethylamine	90:10 v/v	225	1.2			50-150	8.705	bulk, tablet	42
15	Zodiac C18	methanol and water	95:5 v/v	257	1	0.008	0.024	10–50	2.551	bulk, tablet	43
16	Kromasil C18, column	0.01M potassium dihydrogen orthophosphate buffer (pH 4):	50:50 v/v	250	1	0.95	0.24	62.5–375	2.289	bulk, tablet	44

		acetonitrile									
17	Kinetex C8 column	0.2% HSA, pH 2.7 + acetonitrile	gradient elution	243	0.8	0.11	0.34	50 -180	21.02	bulk, cream	45
18	MOS-1 Hypersil C18 column	methanol and phosphate buffer	95:5 v/v	210	0.7	0.2	0.6	1.0–50.0	6.07	tablet, capsule,human plasma	46
19	Zodiac C18	Ortho phosphoric acid buffer, PH 2.5 and Acetonitrile	82:18v/v	255	1	0.00437	0.001326	29 -348	7.302	bulk,tablet ,cream	47
20	phenomenex C18	Buffer 0.1%OPA: Methanol	60:40v/v	245	1	0.94	2.86	31.25-187.5	2.331	bulk, tablet	48
21	C18 column	acetonitrile and water	40:60 v/v	224	–	–	0.1	100–3000	–	rat tissues	49
22	BDS Hypersil C18 column	buffer, methanol and acetonitrile	gradient elution	280	0.8	–	–	50-150	27.2	bulk, cream	50
23(a)	Symmetry Shield RP18	water, phosphoric acid, triethylamine (pH 3.0), with acetonitrile	65:35, v/v	224	1.1	0.005	0.005	5–1500	6.3	plasma	51
23(b)	Symmetry Shield RP18	water, phosphoric acid, triethylamine (pH 3.0), with acetonitrile	65:35, v/v	224	1.1	0.0025	0.005	1–25	6.3	saline	51
24	Neosphere C18	methanol: 0.5% Triethanolamine	–	250	1.2	0.22	0.66	2–12	4.13	bulk, tablet	52
25	YMC, C18 column	Acetonitrile: Buffer 0.1 TEA%	80:20, v/v	224	1	1.57	4.79	30-80	15.38	bulk, tablet	53

		(adjusted pH: 10)									
26	Phenomenex C18	Buffer 0.01N KH2PO4: acetonitrile	65:35v/v	270	1	0.78	2.37	31.25-187.5	2.221	bulk, tablet	54
27	Enable C18	Acetonitrile:0.1% Orthophosphoric Acid pH3	67:33 v/v	242	1	0.631	0.0378	0.5-16	2.2	bulk,tablet, cream	55
28	RP C18	Methanol: Water	08:20 v/v	282	1	0.204	0.62	80-160	5.84	bulk, tablet	56

[57] TBHCL in bulk and pharmaceutical formulation was studied to work on green chemistry by decreasing run time and solvent use. Column used was Waters Acquity UPLC BEH C18, gradient mode with 2.5 min of runtime using mobile phase water: acetonitrile 50:50 v/v with flow rate of 0.6 ml/min. UV detection wavelength was 222nm. Linear range of 25-150 % and recovery was found to be 97.66% - 98.53%.

[58] A stability indicating UPLC method for the estimation of terbinafine hydrochloride (TBHCL), mometasone furoate (MMF), nadifloxacin (NAD), methyl paraben (MP), and propyl paraben (PP) in a topical formulation was developed. The analysis used Waters Acquity UPLC ethylene conjugated hybrid C18 column (50 × 2.1 mm, 1.7 µm). Buffer (pH 3.5): acetonitrile in gradient mode with 0.4 mL/min flow rate at 255 nm was used for elution within 9 min. The RT of TBHCL were observed at 6.0min. Linear fit was observed at 50–150% with LOD of 2.48 ug/ml and LOQ of 7.51 ug/ml.

[59] Bioanalytical analysis of TBHCL from human plasma using ZORBAX SB-Aq C18 column and mobile phase consisted of 50% H3PO4: Acetonitrile in ratio 40:60 v/v at 0.3 mL/min flow rate using paraben as the internal standard (IS). Detection was carried out at 224nm wavelength. The linearity range was established from 0.05 - 2.0 µg/mL with a LOQ of 0.05 µg/mL. Retention time for TBHCL was established at 2.67 minutes.

[60] Simultaneous analysis of terbinafine, N-desmethylcarboxy terbinafine (terbinafine metabolite) and other drugs in presence of their metabolites from human plasma and urine using the UHPLC -UV method is proposed in this study. Samples from plasma and urine were obtained by solid-phase extraction and protein precipitation with very less quantities. Hypersil GOLD C18 column (50 mm x 2.1 mm, 1.7 µm) was used as the stationary phase and acetonitrile: 0.1% formic acid was the mobile phase composition. RT for the determined compound was 3.3 min with correlation coefficient more than 0.994 with good linearity. LOD values differ from 0.01 to 0.07µg/ml for all the compounds.

Sr. No.	**Column**	**Mobile phase (MP)**	**Proportion of MP**	**Detection Wave length**	**Flow rate**	**LOD (µg/mL)**	**LOQ (µg/mL)**	**Linear range**	**RT (min)**	**Application**	**R**
1	Waters Acquity UPLC BEH C18 column	Acetonitrile: water	50:50 v/v	222	0.6 ml/min	–	–	25-150 %	1.66	bulk drug and tablet	5
2	Waters Acquity UPLC ethylene bridged hybrid C18	buffer (pH 3.5): acetonitrile	gradient	255	0.4 mL/min	2.48	7.51	50–150%	6	bulk drug and cream	5
3	ZORBAX SB-Aq C18 column	50% H3PO4:	40:60, v/v	224	0.3mL/min	–	0.05	0.05 - 2.0 µg/mL	2.67	Human plasma	5

		acetonitrile									
4	Hypersil GOLD C18	0.1% formic acid and acetonitrile	–	–	–	0.01 to 0.07	–	–	3.3	Plasma and urine	

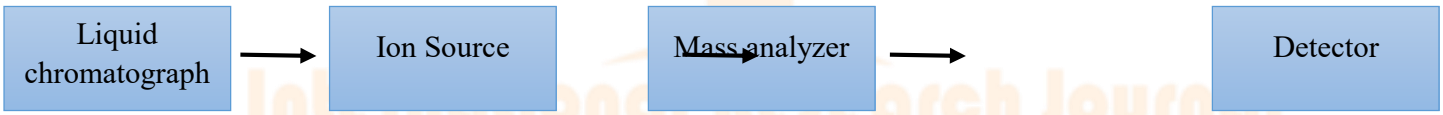
Introduction to LC-MS

LC-MS is the abbreviation of Liquid chromatography-mass spectrometry which is a combination of two techniques for the analysis, isolation, quantification of the substance which is desired from the mixtures. The principle involved in the method is same as HPLC with the mass spectra of the MS. LC make use of the physico-chemical properties of the substance while the MS uses the mass to charge ratio, thus this dual action makes the system more efficient. Molecular mass, structural information is gained by the mass spectra along with the retention time based qualitative information using the LC detectors making the method powerful. The method has many benefits like the selectivity, sensitivity, good speed but the method is expensive, complex and has a limited dynamic range. [92]

Key stages of the analysis are as follows:

- Sample collection
- Calibration and quality control of samples
- Sample extraction and preparation
- Analysis
- Data processing
- Reporting

Instrumentation of LC-MS



Various LC/MS/MS methods used for the method development and validation of Terbinafine HCL in various articles are as follows:

[61] LC-MS/MS method developed for TBHCL quantification in human plasma was fully automated and high-throughput. Bioequivalence study was reliable in determination of TBHCL after administration of 250 mg tablet. Liquid–liquid extraction (LLE) for plasma samples in 2.2 mL 96-deepwell plates was used. A mixture of hexane: methyl *t*-butyl ether (30:70, v/v) was used for extraction of the internal standard (IS) *N*-methyl-1-naphthalenemethylamine from human plasma by. Robotic liquid handling workstations were in process. Using multiple reaction monitoring and positive ion electrospray ionization reversed-phase LC-MS/MS, sample analysis was done. Sample preparation time was very less and 2.2 min was a chromatographic run time. Linear range of concentrations 5.0–2000.0 ng/mL determined from the calibration curve.

[62] Human hair was hydrolysed in 0.5 mL of 5 N NaOH for 1.5 hours for collection of sample of TBHCL. The aqueous layer formed was thus extracted with 1.5 mL of n-hexane for first time and then was injected for analysis by liquid chromatography/tandem mass spectrometry (LC/MS/MS) onto a reversed-phase microbore column. The instrument was operated in the positive ion mode detection and was well equipped with an electrospray ionization interface. 10 mg of human hair extraction showed lower limit of quantitation of 10 ng/g with excellent specificity and ruggedness.

[63] The proposed LC-MS/MS method shows precise drug content uniformity of split tablets of finasteride (FIN) and TBHCL. High standard deviation beyond the accepted value defies the unequal distribution of the drug on the split tablets thus recommended not to split non-scored tablets. Two medications were randomly selected from

that thirty tablets each were separated and divided into 3 groups and weighed. Group 1 of 10 tablet intact, Group 2 of 10 tablet were split into halves, Group 3 of 10 tablet were split into quarters and all were weighed separately. A water: methanol mixture (4:1 v/v) was used for dissolution of all tablets. Agilent eclipse plus C8 analytical column 1200 HPLC system which was coupled with an Agilent 6410 triple quadrupole mass spectrometer was used for LC/MS separation. Mobile phase composed of acetonitrile mixed with water(A) and water containing 0.1% formic acid and 5mM ammonium formate pH 7.5(B) in a ratio 45:55 with 0.8 ml/min flow rate. Concentration range of 20 - 100 ng mL/1 gave a good linear fit with a correlation coefficient 0.999 for FIN and 0.998 for TBHCL. Positive ionization mode was used for MS detection with analyte quantitation monitored by multiple reaction monitoring.

[64] Analytes such as fluconazole, terbinafine, N-desmethyl-carboxyterbinafine, tebuconazole, epoxiconazole, propiconazole and N-deacetyl ketoconazole present in the aqueous environment were quantified from river water along with their metabolites. Chiral chromatography coupled with triple quadrupole tandem mass spectrometry is used as a newer method for separation of chiral and achiral antifungal agents listed above along with their metabolites in environmental matrices.Using positive ion electrospray ionization, multiple reaction monitoring chiral LC-MS/MS, sample analysis was done. The method accuracy was 61%–143%, with good linearity range, r2 value > 0.997. The precision was 3–31% with low (ng L1) MQLs for most analytes.

[65] The method is proposed for the determination of TBHCL in human nail hydrolysate using the Shimadzu 10ADvp HPLC Column which was Aquasil C18 (30 x 2.1 mm, 3µm). The mobile phase selected were of two types, for isocratic elution Acetonitrile: 10 mM Ammonium acetate (pH 5.8) in the ration of 20:80, v/v. For the Gradient Program (B) Acetonitrile was used as mobile phase with flow rate of 0.30 mL/min) Time (min) 0.01 ,1.50 ,2.00 ,2.01 ,5.00 along with % of B mobile phase 65,85, 85, 65 respectively. The applied Biosystem/MDS-Sciex API 3000 or API 4000. The Polarity was positive ionization and scan type was Multiple Reaction Monitoring Terbinafine was monitored from 292 → 141 m/z. The method was linearly validated over a range of 0.500 to 60.0 ng/mL. For the first three validation batches correlation coefficient values were 0.997 or better.

[66] The method is discussed for analysis of terbinafine in human and minipig plasma using turbulent flow chromatography (TurboFlow LC/MS/MS) coupled to mass spectrometry. The chromatographic peak and increased throughput were showed using this direct method which was developed and validated. Stable isotope labelled terbinafine was used as the internal standard and it utilizes positive-ion mode for monitoring of drug. After the acetonitrile protein precipitation, the supernatant without filtration was directly injected onto the LC column. The retention time was approximately found to be 4.3 min. The plasma sample volume of 0.08 ml displayed the lower limit of quantitation (LLOQ) of 0.0679 ng/mL in human and minipig. The relative recoveries gave the value of Interday and intraday accuracy and precision.

[67] Method demonstrated bioequivalence study in terms of rate and extent of absorption of two tablet formulations of terbinafine. Process was based on liquid chromatography with ESI+and tandem mass spectrometry. Naftifine as internal standard was used for detection of terbinafine in human plasma. Study was carried out by administrating 250 mg oral dose of TBHCL in 24 healthy male and female subjects. The total elution chromatographic run time was 5 min and was linear fit in the range of 1.0 to 2000 ng/mL, with LOQ of 1.0 ng/mL.

[68] These studies an efficient and non-invasive strategy for detection of molecular information of the ingested drug of TBHCL and their metabolites in human skin. Sample analysis was detected with thermal desorption-electrospray ionization tandem mass spectrometry (TDESI/MS/MS) in positive ion mode to detect trace terbinafine, secreted in subject's skin after oral administration of terbinafine tablets. Water in 0.1% of acetic acid and methanol were the used solvents in this method LOD value was found between 0.1 and 0.5 ng/ml, with a calibration curve range of 1-100 ng/ml. Samples such as sebum sweat tissue etc collected from different skin regions were directly detected for terbinafine ion and the signals were analysed for eight weeks.

[69] TBHCL in the epidermal skin region was determined using the combination of micro spotting, IS, matrix sublimation by quantitative mass spectrometry imaging. The effect of the addition of the penetration influencer (dimethyl isosorbide (DMI)) was studied and data was compared with LC/MS/MS measurements. Method developed with Xevo G2-XS QT using ionization mode ESI+. Solvents used were ultrapure water and acetonitrile. The values of LOD and LOQ were 1.3ng/ml and 3.93ng/ml respectively.

[70] The unique pharmacokinetic property that is accumulation in skin of TBHCL enhance its efficacy as topical agent and decrease systemic side effects. The study helps to determine TBHCL formulation in vitro by human skin and to measure the concentrations in exposed skin after extraction. After 24 hours exposure of skin to 3 formulations the mean TBHCL concn. were found to be 3.589, 1.590 and 4.219 ug/ml respectively. Electrospray chemical ionization mode was incorporated with Water Micromass, Quatro Micro EScl mass spectroscopy using solvents methanol, 0.1 % Formic H+ in deionised water, the LOD was 10ng/ml.

[71] This method was learnt for the bioequivalence study of terbinafine hydrochloride tablets (125 mg) in plasma of 84 healthy Chinese subjects. The acetonitrile protein precipitation method was used and Terbinafine-d7 as the internal standard (IS). Plasma samples were separated with a C18 chromatographic column, gradient elution program with a flow rate of 0.8 mL/min; using the following mobile phases; 0.1% formic acid in water (A), and methanol (B). System used positive electrospray ionization for quantification which contains multiple reaction monitoring transitions of *m*/*z* 292.5 → 141.1 for terbinafine. The linearity range displayed 2.00–1200 ng/mL, with the accuracy deviation of −6.5% to 10.2%, coefficient of variation was found to be <8.2%.

[72] The developed method was used for clinical samples and showed improved extraction efficiency and long-term stability of plasma results without any internal standard response. Most of the LC–MS/MS assays were based on analyte/IS response ratios for its quantitation, but this method shows IS stability with negligible variation during the anaylsis which shows that the method is reliable and has high-throughput. Method uses naftifine as internal standard (IS) for determination of terbinafine in human plasma. Chromatographic separation was done on a Hypurity Advance column. All compounds were eluted within 2 minutes. Positive multiple reaction monitoring mode with a heated nebulizer was used with transitions m/z 292.2 →141.1 for TBHCL. A mean recovery of 84.3% was found (CV < 4%) with no compromisation of sensitivity The LOQ was found to be 5.11 ng/mL with a good linearity over the range of 5.11–3014.19 ng/mL.

S.No.	Method Detection	Mass spectrometer	Solvent	LOD (ng/mL)	LLOQ (ng/mL)	Linear range (ng/mL)	Application	Ref no.
1	positive ion electrospray ionization	multiple reaction monitoring	methyl *t*-butyl ether and hexane	–	–	5.0–2000.0	Human plasma	61
2	Positive ion mode detection	–	NaOH n-hexane formic acid	–	0.01	–	Human hair	62
3	positive ionization mode	Agilent 6410 triple quadrupole	water, methanol,acetonitrile	5.8	17.58	20-100	bulk,tablet	63
4	ESI+ mode	triple quadrupole, Xevo TQD (chiral)	methanol, acetonitrile and DMSO	0.002	0.01	0.01–1000	aqueous environmental matrices	64
5	positive ionization mode	Biosystem/MDS-Sciex API 3000	ACN/10 mM Ammonium acetate		0.5	0.500 to 60.0	human nail	65
6	Positive ion mode Monitorin	Turboflow LC/MS/MS	–	–	67.9	–	Human and minipig plasma	66
7	Positive ion mode detection	triple quadrupole	–	1	–	1.0 to 2000	Human plasma	67
8	positive ion mode	TDESI/MS/MS, Ultivo	methanol/ water 0.1% acetic acid	between 0.1 and 0.5		1–100	skin, sebum	68
9	ionization mode ESI+	Xevo G2-XS QT	ultrapure water and acetonitrile	1.3	3.93	–	bulk ,skin	69

10	Electrospray chemical ionization	Water Micromass, Quatro Micro ESCl	MeOH, 0.1 % Formic H+ in deionised water	10	–	–	powder, cream, skin	70
11	positive electrospray ionization	multiple reaction monitoring (MRM)	0.1% formic acid in water and methanol	–	–	2.00–1200	Human plasma	71
12	positive multiple reaction monitoring mode	–	–	–	5.11	5.11–3014.19	Human plasma	72

Introduction to Gas Chromatography

GC technique is a versatile, efficient and unique which can be used for gaseous substances and volatile components. Gas–liquid chromatography (GLC) was developed by Martin & Synge and then by James & Martin which helped a lot for the separation and analysis of the various components within less time and effectively. Many volatile solids, liquid solutions and gaseous substances can be analysed directly or by derivatization or pyrolysis by GC. The principle involved in the GC is same as the liquid chromatography that greater the affinity of the compound the greater is retention time thus delayed elution. The method helps to reduce the cost and time required for the separation along with the better precision, ruggedness, more throughput, etc. Carrier gas are used in this technique for the elution along with the most common Flame ionization detector or others too.[93]
Method development by GC can be done as follows:

- Studying Physicochemical properties of drug.
- Selection of chromatographic conditions.
- Developing the analysis approach
- Sample preparation using appropriate diluent
- Method optimization
- Method validation with various parameters

Few GC methods used for the method development and validation of Terbinafine HCL in various articles are as follows:

[73] Terbinafine HCl (TBHCL) concentration in various biological samples can be estimated with many chromatographic methods that exist. In this article a comparison and evaluation of high-performance liquid chromatographic (HPLC) method and a gas chromatographic (GC) is done to check levels of TBHCL in cat hair. 25 ng/mL was sensitivity of the GC method with LOQ of 625 ppb. Compared to HPLC method it was much lower. The sample was eluted by using Capillary HP-5 column and FID as the detector. Still the GC method can be used to determine TBHCL in a linear range of concentrations in cat hair. The final recovery was 70% only and reproducibility of TBHCL in cat hair samples was 95.3%. Basic chromatographic equipments are involved in both the methods for evaluation of drug effectiveness in cat hair sample.

[74] This method uses a green gas chromatographic which is easy and environmental-friendly way to quantify TBHCL in bulk and tablet. Terbinafine HCl (TBHCL) is estimated in a tablet dosage form where an eco-friendly technique of gas chromatography was used along with flame ionization detector. The melting point of the drug is in the range of 204°C–208°C which shows the volatile characteristic of that drug. Zebron DB column was used to separate the TBHCL. Nitrogen carrier gas was used for the analysis. The temperature program-based study with changes in temperature from 230°C to 240°C with a ramp rate of 5°C/min and retained for 2 minutes, again temperature was raised to 250°C with a ramp rate of 3°C/min. This led to the total run time of 10.33 min and at 8.5 min the drug was elute out. The linearity range of 10–60 µg/ ml was recorded along with LOD of 0.88 µg/ml and LOQ of 2.69 µg/ml for TBHCL. Also, the evaluation of TBHCL in tablet dosage forms along with its degradation products were carried by stability studies.

S.No.	Detection column	Dectector	Carrier Gas	LOD (ug/mL)	LOQ (ug/mL)	Linear range (ug/mL)	Retention time	Application	Ref no.
13	Capillary HP-5 column	FID Detector	helium gas	–	0.0006 mg/g	0.025–5	–	cat hair	73
14	GC Shimadzu ,Zebron DB column	FID detector	Nitrogen gas	0.88	2.69	10–60	8.5 min	bulk, tablet	74

Introduction to High performance thin-layer Chromatography

Since the standard and sample chromatography is done parallel, HPTLC has been used as the fastest chromatographic method. In this method all the procedures are performed individually thus it is flexible. Also the system uses very low amount of the stationary as well as the mobile phase the cost per sample analysis is reduced. Principle of adsorption is the basis of HPTLC. Analytes move through the adsorbent depending upon their affinity and the mobile phase runs with the help pf capillary action. The stationary phase is disposable which prevents the sample residue cleaning as in HPLC and the results can be visible to the naked eyes too, which makes it unique. Post-chromatography derivatization (PCD) is easy and can be routinely performed in any lab, which helps to get the additional data such as to lower limit of detections, detect specific functional groups, universal detection, etc. Stationary phase uses materials like alumina, Kieselguhr, Silica gel (most common) coated on plate which can be used horizontally or vertically and many organic /inorganic solvents can be used as mobile phase with linear, circular, anti-circular movement. Isocratic or gradient methods can be used. For the chamber saturation the gas phase, its pH, humidity etc plays an important role in HPTLC.[94]

Steps involved in HPTLC are as follows:

- Selection of chromatographic layer
- Sample and Standard Preparation
- Activation of pre-coated plates
- Selection of mobile phase
- Pre- conditioning (Chamber saturation)
- Application of sample and standard
- Chromatographic development and drying
- Derivatization
- Auto Spray Loading
- Detection and visualization
- Quantification
- Scanning densitometry

Some HPTLC methods used for the method development and validation of Terbinafine HCL in various articles are as follows:

[75] HPTLC method uses silica gel 60 F254 TLC plates backed with aluminium to analyse TBHCL in its tablet formulation. The plate was prewashed with methanol. 1:1:8:0.1 v/v/v/v ratio of Acetonitrile: 1, 4 dioxan: Hexane: Acetic acid was used as the mobile phase. In Camag chamber the developing solvent was run upto 70 mm. Camag TLC scanner-3 was employed for the densitometric scanning at detention wavelength of 282 nm. TBHCL showed a good linear range from 500-4500ng/spot with a Rf value of 0.45.

[76] Method includes the analysis of TBHCL with its degradation products using HPTLC in bulk and tablet.It employs n-hexane: acetone: glacial acetic acid (8:2:0.1v/v) as mobile phase and stationary phase was pre coated silica gel 60F 254 aluminum foil TLC plates. Correlation coefficient was found to be 0.9997 with Rf value of 0.42 a band was shown. Camag TLC scanner at 223nm was used for analysis with concn. range of 200-1000ng/spot The LOD and LOQ was 1.204 ng/ spot and 3.648 ng /spot respectively.

[77] Proposed method using HPTLC was applied for the determination of TBHCL in cream preparation. At 248 nm densitometric scanning was done by using Merck precoated silica gel plate 60 F254 and mobile phase in ratio of 8: 4: 0.1 v/v of Toluene: Ethyl acetate: GAA. The detection limit was 42.22 ng/spot and quantification limit was 127.93 ng/spot along with Rf value of 0.62. A linear response was found at concentration range of 1000–3000 ng/band with regression coefficient of 0.999.

[78] Four drug combination of Ofloxacin, Terbinafine hydrochloride, Tinidazole and Clobetasol propionate were studied by HPLC and HPTLC in topical dosage form. Chromatographic separation by HPTLC was done using precoated silica 60F254 plates as stationary phase and mobile phase was methanol: triethylamine: formic acid: toluene: ethyl acetate in ratio of 1:0.3:0.3:5:4 at 238 nm as lambda max. Method showed recovery more than 99.5% and linearity coefficient more than 0.998. T-test was used to compare assay results statistically which showed p value > 0.05.

[79] This paper discusses HPTLC method for estimation of Mometasonefuroate and Terbinafine hydrochloride (TBHCL) in cream. Stationary phase consists of Merck aluminium backed silica gel 60 F254 plates for TLC. In reflectance/absorbance mode 258nm wavelength with mobile phase of n-hexane: ethyl acetate: acetic acid in ratio of 7.5:3:0.5 v/v/v was used. The Rf value of 0.74±0.02 and linearity range of 400-3600 ng/band was estimated for TBHCL. formulation analysis showed 1.01 ± 0.005% (w/w) of TBHCL with recovery of 101.05 % for TBHCL, respectively.

[80] Stability-indicating HPTLC method which can easily separate the drug from its degradation products has been developed for TBHCL analysis in bulk and formulation. The separation was carried out using toluene, ethyl acetate, formic acid (4.5:5.5:0.1 v/v/v) as mobile phase and Al backed silica gel 60F254 plates. Analysis with densitometric method at 284 nm showed a Rf value of 0.31 ± 0.02 and percent recovery 97.6–101.6, linear regression if 0.9985 and LOQ of 35 ng/band and LOD of 10.5 ng/band.

[81] The three methods were successfully used for the determination of terbinafine hydrochloride and triamcinolone acetonide from a mixture. First derivative (D (1)) spectrophotometric technique was method one with 297nm for TBHCL over concn. range of 5-30 ug/ml and average percentage accuracy of 99.90+/-0.67. Ratio-spectra 1st derivative (RSD (1)) spectrophotometry was another method with 298 nm, average percentage accuracy of 100.22+/-0.51 for TBHCL. TLC of TBHCL depending on quantitative densitometric evaluation over the concentration ranges of 5-25 ug/spot and average percentage accuracy of 100.66+/-0.51 was determined from the method.

[82] TBHCL along with its photodegradation products were studied using 2 different chromatographic methods. One of the methods used was liquid chromatography and the another was TLC fractionation. Stationary phase used for the TLC was Silica gel 60F254 with 12: 0.1:0.1 v/v/v ratio of chloroform, methanol,25% aq. Ammonia respectively. Direct scanning method was used at 284nm with significant stability indication.

Sr. No.	Stationary phase	Mobile phase (MP)	Proportion of MP	Detection Wavelength(nm)	LOD (ng/spot)	LOQ (ng/spot)	Linear range (ng/spot)	RF value	Application	Ref no
1	Aluminium backed silica gel 60 F254	ACN:1,4dioxan:Hexane:Acetic Acid	1:1:8:0.1 v/v/v	282	298.62	385.9	500-4500	0.45	bulk, tablet	75
2	Silica Gel 60F254	n hexane:Acetone:GAA	08:02:0.1 v/v	223	1.204	3.648	200-1000	0.42	bulk, tablet	76
3	Silica Gel Aluminium Plate 60F254	Toluene:EthylAcetate: GAA	08:04:0.1 v/v/v	248	42.22	127.93	1000-3000	0.62	bulk, cream	77

4	silica 60F254	toluene:ethyl acetate:methanol:triethylamine:formic acid	5:4:1:0.3:0.3 v/v/v/v/v	238	–	–	–	–	cream	78
5	silica gel 60 F254	n-hexane: ethyl acetate: acetic acid	7.5:3:0.5 v/v/v	258	125.78	381.15	400-3600	0.74	bulk, cream	79
6	silica gel 60F254	toluene:ethyl acetate:formic acid	4.5:5.5:0.1 v/v/v	284	10.5	35	200–1000	0.31 ± 0.02	bulk, cream, tablet	80
7	spectrodensitometric	–	–	283	–	–	500-2500	–	Pharmaceutical preparations	81
8	silicia gel 60F254	chloroform+methanol +25% aq. ammonia	12: 0.1:0.1 v/v/v	284	–	–	–	–	Bulk , degradation products	82

Terbinafine marketed formulations with strength

Sr no	Brand name	Content with strength	Dosage form
1	Terbinaforce	Terbinafine HCL-1%	Cream
2	Solyster	Terbinafine HCL-1%	Cream
3	Lamisil	Terbinafine HCL-250 mg	Tablet
4	Terbest	Terbinafine HCL-1%	Cream
5	Terbijohn-500	Terbinafine HCL-500 mg	Tablet
6	Tervis	Terbinafine HCL-1%	Lotion
7	Terkey	Terbinafine HCL-500 mg	Tablet
8	Reterb	Terbinafine HCL-1%	Dusting powder
9	Daskil	Terbinafine HCL-1%	Cream
10	Tyza	Terbinafine HCL-1%	Dusting powder
11	Tyza M	Terbinafine HCL-1%	Gel
12	Fungotek	Terbinafine HCL-250 mg	Tablet
13	Terfin F	Terbinafine HCL-1%	Lotion
14	Terfin	Terbinafine HCL-1%	Spray
15	Zimig	Terbinafine HCL-250 mg	Tablet
16	Fungisil	Terbinafine HCL-250 mg	Tablet
17	Terbitotal 500	Terbinafine HCL-500 mg	Tablet
18	Terbicip	Terbinafine HCL-1%	Spray
19	Tebif	Terbinafine HCL-1%	Gel
20	Terwel	Terbinafine HCL-1%	Lotion

Overview

Various analytical methods for the quantification and qualification of terbinafine has been listed in this review individually or along with other drug combination. Some articles show different methods incorporated in the same to comparatively study different techniques. Variables found were the stationary phase, its length, particle size, proportion of mobile phase, its constitution and some similarities were found in the techniques. Various trials were done to optimize the method to give the best suited results. Many further researchers will get a brief idea of the various technique and their methods already developed from this review and thus can go with the further research of terbinafine hydrochloride. In addition to single drug profile records, review also includes records of comparative investigations of one or more compounds belonging to the same class or different. Above official identification procedures for quantitative and qualitative estimation techniques are essential, but for studies involving several components, the prior analytical records serve as a reference for choosing the right procedures,

tools, and solvents. Thus, the review would be beneficial at various stages of drug development such as in process API making, formulation making, formulation evaluations etc.

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