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Review Article

ESTIMATION OF CLOTRIMAZOLE, CLINDAMYCIN PHOSPHATE AND TINIDAZOLE BY VARIOUS ANALYTICAL METHOD: REVIEW ARTICLE

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ABSTRACT

A*nalytical method development and its validation is an important aspect in drug discovery process. Development of analytical method producing accurate and precise data is necessary to ensure the quality and safety of the drugs. At present, the most common analytical method employed for estimation of drugs is Reverse Phase High Pressure Liquid Chromatography (RP-HPLC) because of its high sensitivity, accuracy and speed. Different types of analytical methods are available for estimation of Clindamycin Phosphate, Clotrimazole and Tinidazole including RP-HPLC. This review article briefly discusses analytical methods available for the estimation of Clindamycin Phosphate, Clotrimazole and Tinidazole individually, in combination with other drugs as well as in combine dosage form.*

KEYWORDS: *Analytical methods, RP-HPLC Method.*

INTRODUCTION

Vaginal Discharge Disorder - Vaginal discharge is a mix of fluid and cells from the vagina that varies from whitish and sticky to clear and watery, possibly associated with an odour. It is most often a normal and regular occurrence. However, there are certain types of discharge that can indicate an infection. Abnormal discharge may be yellow or green, chunky in consistency, or foul smelling. Yeast or a bacterial infection usually causes abnormal discharge.

Clindamycin Phosphate is chemically {[(2R,3R,4S,5R, 6R)-6-(2-chloro-1-{[(2S,4R)-1-methyl-4-propyl pyrrolidin-2-yl]formamido}propyl)-4,5-dihydroxy-2-(methyl sulfanyl)oxan-3-yl] oxy}phosphonic acid. It is Lincosamide Antibiotic belonging to class of Carboxylic acids and derivatives. Clindamycin Phosphate inhibits protein synthesis of bacteria by binding to the 50S ribosomal subunits of the bacteria. Specifically, it binds primarily RNA subunit.

Clotrimazole is chemically 1-[(2-Chlorophenyl) (diphenyl) methyl]-1H-imidazole. It is an Imidazole containing Antifungal drug. Clotrimazole interacts with yeast 14-α demethylase, a cytochrome P-450 enzyme that converts lanosterol to ergosterol, an essential component of the membrane. In this way, clotrimazole inhibits ergosterol synthesis, resulting in increased cellular permeability. Clotrimazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms and the uptake of purine, impair triglyceride and/or phospholipid biosynthesis, and inhibit the movement of calcium and potassium ions across the cell membrane by blocking the ion transport pathway known as the Gardos channel.

Tinidazole is chemically 1-(2-ethylsulfonylethyl)-2-methyl-5- nitro-imidazole. It is a prodrug and antiparasitic drug used against protozoan infection. The nitro group of tinidazole is reduced in *Trichomonas* by a ferredoxin-mediated electron transport system. The free nitro radical generated as a result of this reduction is believed to be responsible for the antiprotozoal activity. It is suggested that the toxic free radicals covalently bind to DNA, causing DNA damage and leading to cell.

Aim of the review article is to briefly discuss the analytical methods available for the estimation of Clindamycin Phosphate, Clotrimazole and Tinidazole in bulk, in combined dosage form and in various formulations with other drugs mainly focusing on the mobile phase, stationary phase and detector type.

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Various analytical methods for estimation of the drugs:

Table No. 1: Official method for Clindamycin Phosphate [16-18]

Sr. No	Official in	Method	Description	Ref. No
1	IP-2010	Clindamycin Phosphate (Bulk drug)	**Mobile phase:** Acetonitrile: Phosphate Buffer, pH 2.5 (20:80) **Column:** C_8 (250 × 4.6 mm i.d., 5µ) **Wavelength:** 210 nm. **Flow rate:** 1.0 ml/min	[16]
2	BP-2015	Clindamycin Phosphate (Bulk drug)	**Mobile phase:** Acetonitrile: Phosphate Buffer, pH 2.5 (20:80) **Column:** C_8 (250 × 4.6 mm i.d., 5µ) **Wavelength:** 210 nm. **Flow rate:**1.0 ml/min	[17]
3	USP30-NF25	Clindamycin Phosphate (Bulk drug)	**Mobile phase:** Buffer: 0.35% v/v o-Phosphoric acid, pH 3.69 Organic solution: Methanol: Acetonitrile (10:90) Sol-A: Buffer: Organic solution (92:08) Sol-B: Buffer: Organic solution (52:48)	[18]

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0	95.0	5.0	Equilibrium
0-40	95.0-5.0	5.0-95.0	Linear gradient
40-41	5.0-95.0	95.0-5.0	Linear gradient
41-46	95.0	5	Isocratic

Column: C_8 (250 × 4.6 mm i.d., 5µ)
Wavelength: 214 nm.
Flow rate: 1.2 ml/min

Table No. 2: Other reported method for Clindamycin Phosphate [19-34]

Sr. No	Drugs	Method	Brief introduction	Ref. No
1	Clindamycin Phosphate	**RP-HPLC**	**Mobile phase**: Acetonitrile: Phosphate Buffer, pH 2.8 (24:76) **Column**: Luna C_{18}, (250 mm × 4.6 mm, 5µ,) **Flow rate**: 1 ml/min **Wavelength:** 210 nm	[19]
2	Clindamycin Phosphate	**RP-HPLC**	**Mobile phase**: Acetonitrile: Phosphate Buffer, pH 2.5 (30:70) **Column**: Zorbax C_8, (250 mm × 4.6 mm, 5µ,) **Flow rate**: 1 ml/min **Wavelength:** 210 nm.	[20]
3	Clindamycin Phosphate	**RP-HPLC**	**Mobile phase**: Acetonitrile: 0.1 % Phosphoric acid (25:75) **Column**: Bondapack C18, (150 mm × 3.9 mm, 5µ,) **Flow rate**: 0.8 ml/min **Wavelength:** 210 nm.	[21]
4	Clindamycin Phosphate	**RP-HPLC**	**Mobile phase**: Acetonitrile: Carbonate Buffer, pH 10.5 (Gradient mode) **Column**: X-terra RP C18, (100 mm × 4.6 mm, 3.5µ,) **Flow rate**: 1.0 ml/min **Wavelength:** 214 nm.	[22]
5	Clindamycin Palmitate Hydrochloride	**RP-HPLC**	**Mobile phase:** Phosphate: Buffer pH 3.0: Acetonitrile: Tetrahydrofuran, (20:75:5 v/v), **Column**: Phenomenex Zorbax CN (150×4.6mm.5µ) **Flow Rate:** 1 ml/min **Wavelength**: 210nm	[23]
6	Clindamycin Phosphate	**UV-Spectrophotometry**	**Formation and Solving using Water:-** **Wavelength**: 210 nm **Formation and solving using Phosphate buffer saline solution using pH. 6.75**: **Wavelength**: 210 nm **Concentration range:** 5-30 µg/mL	[24]
7	Metronidazol, Clindamycin Phosphate And Clotrimazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 2.4: Acetonitrile (70:30) **Column**: Hypersil BDS C_8 (250× 4.6mm. 5µ) **Flow Rate:** 2.3 ml/min **Wavelength**: 210 nm	[25]
8	Clindamycin and Adapalene	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.0: Acetonitrile (40:60) **Column**: Luna C_{18} (250× 4.6mm. 5µ)	[26]

			Flow Rate: 1.0 ml/min **Wavelength**: 210 nm	
9	Clindamycin Phosphate and Adapalene	**Stability indicating RP-HPLC**	**Mobile phase:** Sol-A: Phosphate Buffer, pH 2.5: Acetonitrile (84:16), Sol-B: Acetonitrile: Tetrahydrofuran (80:20) **Time (Min) / Sol-A (% v/v) / Sol-B (% v/v)** 0 / 100 / 0 8 / 100 / 0 9 / 24 / 76 13 / 24 / 76 14 / 100 / 0 **Column**: X bridge C_{18} (50× 4.6mm. 3.5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 210 nm	
10	Clindamycin Phosphate And Clotrimazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.0: Acetonitrile (48:52) **Column**: Hypersil BDS C_{18} (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 220 nm	[28]
11	Clindamycin Phosphate And Clotrimazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 2.5: Acetonitrile (70:30) **Column**: Hypersil BDS C_8 (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 210 nm	[29]
12	Metronidazole, Clindamycin Phosphate and Clotrimazole	**Stability indicating RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 4.5: Methanol Acetonitrile (30:20:50) **Column**: Hypersil BDS C_{18} (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 210 nm	[30]
13	Clindamycin Phosphate and Miconazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.5: Acetonitrile (65:35) **Column**: Inertsil ODS C_{18} (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 220 nm	[31]
14	Clindamycin Phosphate And Nicotinamide	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.5: Methanol (60:40) **Column**: Hypersil BDS C_{18} (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 210 nm	[32]
15	Tretinoin and Clindamycin Phosphate	**RP-HPLC**	**Mobile phase:** Sol-A: Water: Methanol (50:50), Sol-B: Water: Acetonitrile (50:50) **Column**: Lichrospher C_{18} (250× 4.6mm. 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 210 nm	[33]
16	Tretinoin and Clindamycin Phosphate	**UV Spectroscopy**	**First order Derrivative Method :-** **Wavelength:** 251 nm for Clindamycin Phosphate and 364 nm for Tretinoin **Second Order Derivative Method:** **Wavelength:** 239 nm for Clindamycin Phosphate and 387 nm for Tretinoin **Concentration range:** 60-1200 µg/ml for Clindamycin Phosphate and 1.25-25 µg/ml for Tretinoin **Solvent**: 0.1M NaOH	[34]

Table No. 3: Official method of clotrimazole [35-39]

Sr. No	Official In	Method	Description	Ref. No
1	IP-2010	Liquid Chromatography (Clotrimazole Cream)	**Mobile phase**: Methanol: 0.02M perchloric acid, pH 7.5 (70:30v/v) **Column**: ODS (200× 4.6mm. 5µ) **Wavelength**: 215 nm **Flow rate:** 1.5 ml/min	[35]
2	USP30-NF25 2007	Liquid Chromatography (Clotrimazole Cream)	**Mobile phase**: Methanol: Phosphate buffer (3:1) **Column**: C_{18} (250× 4.6mm. 10µ) **Wavelength**: 254 nm **Flow rate:** 1.5 ml/min	[36]
3	JP-2011	Potentiometry (Clotrimazole Bulk)	**Titrate:** 0.35 gm Clotrimazole in 80 ml Acetic acid **Titrant**: 0.1 M Perchloric acid	[37]

			0.1 M Perchloric acid is equivalent to 34.48 mg of Clotrimazole	
4	BP-2015	Liquid Chromatography (Clotrimazole Cream)	**Mobile phase**: 0.02 M o-Phosphoric acid: Methanol (30:70, pH 7.5) **Column**: C_{18} (200× 4.6mm. 10µ) **Wavelength**: 215 nm **Flow rate:** 1.5 ml/min	[38]
5	EP-2014	Potentiometry	**Titrate:** 0.39 gm Clotrimazole in 80 ml Anhydrous Acetic acid **Titrant**: 0.1 M Perchloric acid 0.1 M Perchloric acid is equivalent to 34.48 mg of Clotrimazole	[39]

Table No. 4: Other reported method for Clotrimazole [40-50]

Sr. No	Drugs	Method	Brief Introduction	Ref. No
1.	Clotrimazole	**Stability indicating HPLC**	**Mobile phase**: Methanol: 0.1% Triethylamine, pH 3.0 (75:25) **Column**: Gracemart C_{18} (150 × 4.6 mm, 5 µm) **Wavelength**: 215 nm **Flow rate:** 1 ml/min	[40]
2.	Betamethasone and Clotrimazole	**HPLC**	**Mobile phase**: Methanol: Acetate buffer, pH 6.8: Acetonitrile (33:27:40, v/v) **Column**: C_{18} (250 X 4.0 mm, 5 µm) **Wavelength**: 254 nm **Flow rate:** 1.5 ml/min	[41]
3.	Clotrimazole and Beclomethasone dipropionate	**HPLC**	**Mobile phase**: Acetonitrile: Water (70:30) **Column**: Kromasil C_{18} (150 mm × 4.6 mm, 5 µm) **Wavelength**: 254 nm **Flow rate:** 1 ml/min	[42]
4.	Clotrimazole and Dexamethasone	**UV-Spectroscopy**	**First order derivative:** **Wavelength:** 239.00 nm, the zero crossing point of Dexamethasone was selected for determination of Clotrimazole and 252.80 nm, the zero point of Clotrimazole was selected for determination of Dexamethasone **Concentration range:** 100-500 µg/ml for Clotrimazole 4-20 µg/ml for Dexamethasone **Solvent**: Methanol	[43]
5.	Clotrimazole and Ketoconazole	**HPLC**	**Mobile phase**: Methanol: Water: Diethylamine: Glacial acetic acid pH 7.0 (80:20:0.3:0.2) **Column**: C_{18} (150 × 4.6 mm, 5 µm) **Wavelength**: 224 nm **Flow rate:** 1 ml/min	[44]
6.	Clotrimazole	**HPTLC**	**Mobile phase**: Cyclohexane: Toluene: Methanol: Triethyleamine (8:2:0.5:0.2 v/v/v/v) **Plate**: Precoated silica gel $60F_{254}$ **Wavelength**: 262 nm	[45]
7.	Clotrimazole And Tinidazole	**RP-HPLC**	**Mobile phase**: Methanol: Acetonitrile (95:5) **Column**: Chromasil C_{18} (250 mm × 4.6 mm, 5 µm) **Wavelength**: 229 nm **Flow rate:** 1 ml/min	[46]
8.	Clotrimazole and its two degradation products	**HPLC**	**Mobile phase**: Acetonitrile: Water (65:35 v/v) **Column**: SB-Phenyl (75mm X 4.6mm) **Flow rate**:- 0.5 ml/min **Wavelength** :- 210nm	[47]
9.	Clotrimazole	**UV-Spectroscopy**	**Solvent**: 1N H_2SO_4 Solution **Wavelength**: λm263 nm **Concentration range**: 4-12 µg/ml	[48]
0	Beclomethasone dipropionate, Clotrimazole, Chloramphenicol and lidocaine	**HPLC**	**Mobile phase**: Sol-A: Acetate buffer, pH 6.4 Sol-B: Acetonitrile **Time (Min) / Sol-A (%) / Sol-B (%)** 0-4 / 65 / 35 4-8 / 65→35 / 35→65	[49]

			8-15	35	65	
			15-20	35→55	65→45	
			20-22	55→65	45→35	
			22-25	65	35	
			Column: C_{18} (250 mm × 4.6 mm, 5 µm) **Wavelength**: 254 nm **Flow rate**: 1 ml/min			
11	Clotrimazole and Tinidazole	**HPTLC**	**Mobile phase**: Toluene: Methanol: Ethyl acetate: Tri ethylamine (5:1:1:0.1v/v/v/v) **Plate**: Precoated silica gel 60F_{254} **Wavelength**: 254 nm			[50]

Table No. 5: Official method of Tinidazole [51-54]

Sr. No	Official In	Method	Description	Ref. No
1	IP-2010	**UV Spectroscopy (Tinidazole Tablet)**	**Concentration:** 15 µg /ml **Wavelength**: 310nm **Solvent:** Methanol	[51]
2	BP-2015	**Liquid Chromatography (Tinidazole Related substance)**	**Mobile phase**: Acetonitrile: Methanol: Water (10:20:70 v/v) **Column**: C_8 (250mm X 3.0mm, 5 µ) **Flow rate**: 0.5 ml/min **Wavelength**: 320nm	[52]
3	USP30-NF14	**Potentiometry titration (Tinidazole Bulk)**	**Titrate:** 0.15 gm Tinidazole in 25 ml Glacial Acetic acid **Titrant**: 0.1 N Perchloric acid 0.1 M Perchloric acid is equivalent to 24.73 mg of Tinidazole	[53]
4	JP-2011	**Potentiometry titration (Tinidazole Bulk)**	**Titrate:** 0.35 gm Tinidazole in 50 ml Acetic anhydride **Titrant**: 0.1 mol/L Perchloric acid Each 0.1mol/L Perchloric acid is equivalent to 24.73 mg of Tinidazole	[54]

Table No. 6: Other reported methods of Tinidazole [55-68]

Sr no.	Drugs	Method	Brief introduction	Ref. No.
1	Ciprofloxacin and Tinidazole	UV Spectrophotometry	**Simultaneous equation method**: **Wavelength:** 272 nm Ciprofloxacin, 365.0 nm Tinidazole **Concentration range:** 2-7 µg/ml for Ciprofloxacin, 4-24 µg/ml Tinidazole **Q- analysis method:** **Wavelength:** Isoabsorptive point at 299 nm, 277nm, λ_{max} of Ciprofloxacin **Concentration range :** 2-7 µg/ml for Ciprofloxacin, 4-24 µg/ml Tinidazole **Solvent:** 0.1N NaOH	[55]
2	Ciprofloxicin And Tinidazole	**RP-HPLC**	**Mobile phase:** Water and Methanol (60:40v/v), **Column:** Inertsil ODS C_{18} (250 X 4.6mm, 5µm) **Flow Rate:** 0.8 ml/min **Wavelength**: 316 nm	[56]
3	Amoxycillin Trihydrate and Tinidazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.6: Acetonitrile (30:70v/v) **Column:** Hiq Sil, C_{18},(250 X 4.6mm, 5µ) column **Flow Rate:** 1.0 ml/min **Wavelength**: 240 nm	[57]
4	Tinidazole And Moxifloxacin	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 4.5: Acetonitrile (80:20v/v) **Column:** Inertsil C18 (250 X 4.6mm, 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 240 nm	[58]
5	Fluconazole and Tinidazole	**RP-HPLC**	**Mobile phase:** Phosphate Buffer, pH 3.25: Acetonitrile (82:18v/v) **Column:** ODS Hypersil C_{18} **Flow Rate:** 1.5 ml/min **Wavelength**: 210 nm	[59]

6	Norfloxacin and Tinidazole	**RP-HPLC**	**Mobile phase:** 0.2% Triethylamine, pH 2.6: Acetonitrile (80:20v/v) **Column:** Shodex C_{18} (250 X 3.9mm, 5µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 311 nm	[60]
7	Norfloxacin and Tinidazole	**UV Spectroscopy**	**Simultaneous Equation Method** **Wavelength:** 273 nm for Norfloxacin and 319 nm for Tinidazole **concentration ranges:** 2.5-20µg/mL for Norfloxacin and 5-40 µg/mL for Tinidazole **Solvent**: Water	[61]
8	Norfloxacin and Tinidazole	**UV Spectroscopy**	**Different Spectroscopy Method** **Wavelength:** 291.6 nm for Norfloxacin and 344.4 nm for Tinidazole **concentration ranges:** 2-20µg/mL for Norfloxacin and 5-50 µg/mL for Tinidazole **Solvent**: 0.1N NaOH	[62]
9	Amoxicillin, Tinidazole And Omeprazole	**RP-HPLC**	**Mobile phase:** Methanol: Acetonitrile: Water (49: 49: 2 % v/v/v) **Column:** inertsil C_{18} (250 × 4.6 mm, 5 µ) **Flow Rate:** 1.0 ml/min **Wavelength**: 230 nm	[63]
10	Omeprazole, Tinidazole and Clarithromycin	**RP-HPLC**	**Mobile phase:** Acetonitrile: Methanol: Buffer, pH 3.5 (33: 17: 50, v/v/v) **Column:** Lichrosorb C8(150 X 4.6 mm, 10µm) **Flow Rate:**1.0 ml/min **Wavelength**: 215 nm	[64]
11	Ofloxacin and Tinidazole	**RP- HPLC**	**Mobile phase:** Ammonium Acetate Buffer pH 4.0, Acetonitrile: Tetrahydrofuran (60:30:10 v/v/v) , **Column**: Intersil ODS C_{18} (250×4.6mm.5µ) **Flow Rate:** 1 ml/min **Wavelength**: 304 nm	[65]
12	Ciprofloxacin HCl and Tinidazole	**RP-UPLC**	**Mobile phase:** Phosphate Buffer, pH 3.0: Acetonitrile (80:20) **Column:** Purospher C_{18} (100×2.1 mm, 2µm), **Flow Rate:** 1.0 ml/min **Wavelength**: 278.5 nm for Ciprofloxacin HCl and 317.5 nm for Tinidazole	[66]
13	Ciprofloxacin and Tinidazole	**UV Spectroscopy**	**Simultaneous Equation method:** **Wavelength**: 271nm for Ciprofloxacin and 318nm for Tinidazole **Concentration range:** 10-35µg/mL for Ciprofloxacin, 10-80 µg/mL for Tinidazole **Q-Absorbance ration method:** **Wavelength**:292nm (iso-absorptive point) and 271nm (λ max of Ciprofloxacin) **Concentration range:** 10-35µg/mL for Ciprofloxacin, 10-80 µg/mL for Tinidazole **Solvent**: Phosphate Buffer, pH 6.8	[67]
14	Ciprofloxacin Hydrochloride, O floxacin, Tinidazole and Ornidazole	**RP-HPLC**	**Mobile phase:** Acetonitrile: Water: Tri ethylamine (25:75:1, pH 6.0) **Column:-** Phenomex C_{18}, (250 X 4.6mm) **Flow Rate:** 1.0 ml/min **Wavelength**:- 300 nm	[68]

Table No. 7: Reported methods of Clindamycin Phosphate, Clotrimazole and Tinidazole in combination [69, 70]

Sr no.	Drugs	Method	Brief introduction	Ref. No.
1	Clindamycin Phosphate, Clotrimazole and Tinidazole	RP-HPLC	**Mobile phase:** Phosphate Buffer, pH 2.5: Methanol (40:60) **Column:-** Kromasil C_{18}, (150 X 4.6mm, 5 µm) **Flow Rate:-** 1.0 ml/min **Wavelength**:- 210 nm	[69]

2	Clindamycin Phosphate, Clotrimazole and Tinidazole	RP-HPLC	**Mobile phase:** Phosphate Buffer, pH 3.0: Methanol (60:40) **Column:-** Shiseido C_{18}, (250 X 4.6mm, 5 µm) **Flow Rate:-** 1.0 ml/min **Wavelength**:- 210 nm	[70]

CONCLUSION

Presented review includes various analytical methods for the determination of Clindamycin phosphate, Clotrimazole, and Tinidazole in various pharmaceutical formulations alone or in combination with other drugs with help of RP-HPLC. For quantitative estimation of Clindamycin phosphate, Clotrimazole, and Tinidazole, RP-HPLC method is the most common among others. All the reported methods are sensitive, precise and accurate; consisting mainly RP C18 column as stationary phase and variety of polar solvents (like methanol, water, acetonitrile, buffers) in different ratios as mobile phase. For development of analytical methods, for newly developed or for upcoming research work, this can be taken for consideration.

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