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A REVIEW ON CHROMATOGRAPHIC AND SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF EZETIMIBE AND FLUVASTATIN

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ABSTRACT

Ezetimibe is selective cholesterol absorption inhibitor. It is an anti-hyperlipidemic agent. It is used in treatment of Hypercholesterolemia. Fluvastatin is a drug which comes under class of statin. It is used to reduce cholesterol levels and prevent cardiovascular disease. It decreases low density lipoprotein (LDL) cholesterol. Ezetimibe plus Fluvastatin was proved to be effective at a dose of 10mg and 80mg in management of hypercholesterolemia compare to Ezetimibe and Fluvastatin Monotherapy. Cholesterol absorption inhibitor plus statin showed the effective results in relief of the Hypercholesterolemia. This article narrate different chromatographic (HPLC, HPTLC) and different spectrophotometric method (UV) for determination of the Ezetimibe and Fluvastatin.

KEYWORDS: Ezetimibe, Fluvastatin, UV- Spectroscopy, HPLC (High Performance Liquid Chromatography), HPTLC (High Performance Thin Layer Chromatography).

INTRODUCTION[1-3]

Ezetimibe is selective cholesterol absorption inhibitor. It is an anti-hyperlipidemic agent. It is used in treatment of Hypercholesterolemia. It inhibits the absorption of cholesterol and decreasing delivery of intestinal cholesterol to the liver. It is metabolized into its glucuronide in liver and small intestine which prevent absorption of cholesterol.

Fluvastatin is HMG-CoA reductase inhibitor.3-Hydroxy 3-methyl glutaryl coenzyme A (HMG-COA) reductase is responsible for converting of HMG-CoA to mevalonate, the rate –

limiting step in cholesterol biosynthesis. It is used to reduce cholesterol levels and prevent cardiovascular disease. It decreases low density lipoprotein (LDL) cholesterol.

Combination of Cholesterol absorption inhibitor and statin found to be effective in reducing Low density lipoprotein cholesterol (LDL-C) and total cholesterol levels. Combination of Ezetimibe and Fluvastatin showed effective result in relief of Hypercholesterolemia.

Reported methods are categorized depending on the following considerations:

1. Single component analyzed by UV-spectroscopy methods and chromatographic method.
2. Analysis of Ezetimibe and Fluvastatin in combination with other drugs by UV-spectroscopy methods and chromatographic method.

Table I: Reported Analytical Method of Ezetimibe[4-15]

Sr. No	Drug	Method	Description	Ref No.
1	Ezetimibe in tablet dosage form	UV-Spectroscopic	**Detection:** 252nm **Correlation Co-efficient:** 0.998 **Linearity Range:** 2-20µg/ml **% Recovery:** 100.9 to 102.32% **LOD:** 0.10µg/ml **LOQ:** 0.30µg/ml	[4]
2	Ezetimibe in tablet dosage form	UV-Spectrophotometric	**Detection:** 232nm **Linearity range:** 5-30µg/ml **Correlation Co-efficient:** 0.999	[5]
3	Ezetimibe in tablet formulation	Spectrophotometric	**Detection:** 745nm **Linearity Range:** 100-260µg/ml **Correlation Co-efficient:** 0.995	[6]
4	Ezetimibe in Pharmaceutical formulations	Spectrophotometric	**Detection:** 234nm **Linearity Range:** 5-20µg/ml **Correlation Co-efficient:** 0.999 **% Recovery:** 96-98%	[7]
5	Ezetimibe in tablet dosage form	RP-HPLC	**Stationary Phase:** Phenomenex Luna C_{18} column **Mobile Phase:** Acetonitrile: 0.02M Phosphate buffer: Methanol (70:20:10v/v) **Detection:** 235nm **Linearity Range:**10-100µg/ml **Flow Rate:** 1ml/min **Retention time:** 3.537 min **LOD:** 1µg/ml **LOQ:** 3.2µg/ml **% Recovery:** 99.6-101%	[8]
6	Ezetimibe in Human serum	RP-HPLC	**Stationary Phase:** C_{18} Symmetry Shield column **Mobile Phase:** Acetonitrile and 0.1 M Ammonium acetate aqueous solution 55:45 (v/v) **Linearity Range:** 10-800ng/ml **Detection:** 232nm **FlowRate:**0.75ml/min	[9]

			LOD: 4.60ng/ml **LOQ**:13.94ng/ml	
7	Ezetimibe in bulk and pharmaceutical formulation	RP-HPLC	**Stationary Phase:** Kromasil C_8 column **Mobile Phase:** Acetonitrile: 0.02 M Potassium dihydrogen orthophosphate buffer (72:28 v/v) **Detection:**232nm **FlowRate:**1ml/min **Linearity Range**: 10-45µg/ml **Retention time:** 4.24 min **Correlation Co-efficient:** 0.999 **% Recovery:** 99.66% **LOD:**0.0413µg/ml **LOQ:** 0.1253µg/ml	[10]
8	Ezetimibe in tablet dosage form	Stability indicating RP-HPLC	**Stationary Phase:** Zorbax SB C_{18} column **Mobile Phase:** 0.02N Ortho phosphoric acid: Acetonitrile (20:80 v/v) **Detection:** 232nm **Linearity Range:** 1-10µg/ml	[11]
9	Ezetimibe in pharmaceutical dosage form	RP-HPLC	**Stationary Phase:** Betasil C_{18} column **Mobile Phase:** Acetonitrile: 10Mm potassium dihydrogen phosphate (55:45 v/v) **Linearity Range:** 4-24µg/ml **Retention time:** 4.91 min **Flow Rate:** 1ml/min **Detection:**233nm **LOD:** 286.77µg/ml **LOQ:** 869.01µg/ml	[12]
10	Ezetimibe in pharmaceutical formulation tablets	HPLC	**Stationary Phase:** C_{18} column **Mobile Phase:** Acetonitrile: Ammonium acetate (10mM, pH 3.0), (75:25v/v) **Flow Rate:** 1ml/min **Detection:** 240nm **Linearity Range:** 10-60µg/ml **% Recovery:** 95.3% **LOD:** 5µg/ml **LOQ:** 10µg/ml	[13]
11	Ezetimibe in bulk drug and formulation	RP-HPLC	**Stationary Phase:** Agilent XDB C_{18} column **Mobile Phase:** Di sodium hydrogen ortho phosphate buffer: Methanol (32:68v/v) **Detection:** 234nm **Linearity Range:** 20-100µg/ml **Retention time:** 5.7 min **Correlation Co-efficient:** 0.999	[14]
12	Ezetimibe in tablet dosage form	RP-HPLC	**Stationary Phase:** ODS-3V Column **Mobile Phase:** Ammonium acetate buffer: Acetonitrile (45:55v/v) **Flow Rate:** 1.5ml/min **Detection:**230nm **% Recovery:** 98-99%	[15]

Table II: Reported method of Ezetimibe in combination with other drugs.[16-29]

Sr. No	Drug	Method	Description	Ref No.
13	Simvastatin and ezetimibe in bulk drug	Spectrophotometric	**Detection:** 223 and 258 nm **Linearity Range:** 1-25µg/ml **Mean recovery:** 99%-99.6% **Correlation** **Co-efficient:** 0.999	[16]
14	Ezetimibe and Carvedilol	UV spectroscopic	**Detection:** Ezetimibe- 232nm Carvedilol-238nm **Linearity Range:** Ezetimibe- 2-50µg/ml Carvedilol- 2-20µg/ml **LOD:** Ezetimibe- 0.4µg/ml Carvedilol- 1.3µg/ml **LOQ:** Ezetimibe- 0.7µg/ml Carvedilol- 2.1µg/ml	[17]
15	Ezetimibe and Fenofibrate	UV spectroscopic	**Detection:** 286nm and 232nm **Linearity Range:** 2-20µg/ml **%Recovery:** 98% **Correlation** **Co-efficient:** 0.999	[18]
16	Valsartan and Ezetimibe	Spectrophotometric	**Detection:** Valsartan- 425m Ezetimibe- 428nm **Linearity Range:** Valsartan- 5-40 µg/ml Ezetimibe- 1-50 µg/ml **% Recovery:** Valsartan- 99.3% Ezetimibe- 100.3% **Correlation** **Co-efficient:** Valsartan- 0.995 Ezetimibe- 0.999	[19]
17	Simvastatin and Ezetimibe	UV-Spectrophotometric	**Detection:** 235nm and 266nm **Linearity Range:** 2-20µg/ml **% Recovery:** 91-101% **Correlation** **Co-efficient:** 0.999	[20]
18	Rosuvastatin calcium and Ezetimibe in tablet dosage form	RP-HPLC	**Stationary Phase:** Licrosphere C_{18} column **Mobile Phase:** Methanol: Acetonitrile: Phosphate buffer, pH 3.5 (60:20:20 v/v) **Detection:** 279nm **Flow Rate:** 1ml/min **Mean recovery:** 99.01% - 100.64% **Linearity Range:** 5-25µg/ml **LOD:** Rosuvastatin-0.01µg/ml Ezetimibe - 0.004µg/ml	[21]

			LOQ: Rosuvastatin -0.03µg/ml Ezetimibe - 0.01µg/ml	
19	Atorvastatin calcium and ezetimibe as the bulk drug and in tablet dosage forms	HPTLC	**Stationary Phase:** Silica gel 60 F254 **Mobile Phase:** Toluene–Methanol 8:2 (v/v) **Detection:** 240nm **Linearity Range:** 0.4–2.4µg/ml **Correlation** **Co-efficient:** 0.999	[22]
20	Rosuvastatin calcium and Ezetimibe in Pharmaceutical dosage form	RP-HPLC	**Stationary Phase:** C_{18} Column **Mobile phase:** Acetonitrile: Water (75:25 % v/v) **Detection:** 252 nm. **Flow rate:** 0.6 ml/min **Linearity Range:** 5-40µg/ml **Retention time:** Rosuvastatin-2.91 min Ezetimibe-6.53 min **LOD:** Rosuvastatin-0.76 Ezetimibe-0.91 **LOQ:** Rosuvastatin-2.3 Ezetimibe-2.7	[23]
21	Atorvastatin calcium and ezetimibe	RP-HPLC	**Stationary Phase:** Hypersil BDS C_{18} column **Mobile phase:** Phosphate buffer pH-4.5 :Acetonitrile (35:65 v/v) **Detection:** 228 nm **Flow rate:** 1ml/min **Linearity Range:** 12.5-75µg/ml	[24]
22	Simvastatin and Ezetimibe	Stability indicating RP-HPLC	**Stationary Phase:** C_{18} ODS Hypersil column **Mobile phase:** Acetonitrile: Phosphate buffer (pH 4.5, 0.01M) (65:35 v/v) **Detection:** 232nm **Flow rate:** 1ml/min	[25]
23	Atorvastatin and Fenofibrate and Ezetimibe	RP-HPLC	**Stationary Phase:** C_{18} column **Mobile phase:** Methanol: Acetonitrile: Water (80:10:10) **Linearity Range:** Atorvastatin- 3-7µg/ml Fenofibrate- 48-112µg/ml Ezetimibe- 3-7µg/ml **LOD:** Atorvastatin- 0.05µg/ml Ezetimibe- 1.58µg/ml	[26]

			LOQ: Atorvastatin- 0.12µg/ml Fenofibrate- 4.78µg/ml Ezetimibe- 0.15µg/ml	
24	Atorvastatin and Ezetimibe in Human Plasma	Stability indicating RP-HPLC	**Stationary Phase:** X-Terra C_8 column **Mobile phase:** Ortho phosphoric acid: Acetonitrile (40:60v/v) **Linearity Range:** 5-25µg/ml **Detection:** 235 nm **Flow rate:** 1.2ml/min	[27]
25	Atorvastatin and Ezetimibe	RP-HPLC	**Stationary Phase:** ODS C_{18} Column **Mobile phase:** Methanol: Water (90:10v/v) **Linearity Range:** 5-30µg/ml **Detection:** 236nm **Flow rate:** 1ml/min **Retention time:** Atorvastatin- 1.9 min Ezetimibe- 3.46 min **LOD:** Atorvastatin- 5µg/ml Ezetimibe- 10µg/ml **LOQ:** Atorvastatin-10µg/ml Ezetimibe- 20µg/ml	[28]
26	Rosuvastatin and Ezetimibe	RP-HPLC	**Stationary Phase:** C_{18} column **Mobile phase:** Acetonitrile: Water: 0.02M Phosphate buffer pH 8 (40:10:50v/v) **Detection:** 230nm **Flow rate:** 1ml/min **Linearity Range:** 30-90µg/ml **LOD:** Rosuvastatin- 0.05µg/ml Ezetimibe- 0.06µg/ml **LOQ:** Rosuvastatin-0.08µg/ml Ezetimibe- 0.05µg/ml	[29]

Table III: Reported Analytical Method of Fluvastatin.[30-36]

Sr. No	Drug	Method	Description	Ref No.
1	Fluvastatin in Bulk and Pharma-ceutical Formulations	UV Spectro-photometric	**Detection:**304nm **Linearity Range:** 5-25µg/ml **Correlation Co-efficient:** 0.999 **%Recovery:** 98%-101% **LOD:** 0.081µg/ml **LOQ:** 0.246µg/ml	[30]
2	Fluvastatin in Pharma-ceutical Preparations	Spectro-photometric	**Detection:** 462nm **LinearityRange:**15.0–50.0 and 10.0–90.0µg/ml **LOD:** 0.017 and 0.134µg/ml	[31]

3	Fluvastatin in human plasma	HPLC	**Stationary Phase:** C_{18} column **Mobile phase:** Methanol:13 mM tetrabutylammonium fluoride (3:2 v/v) **Detection:** 305 and 380nm	[32]
4	Fluvastatin Sodium in Bulk and Dosage Form	Stability Indicating RP-HPLC	**Stationary Phase:** Phenomenex Luna C_{18} column **Mobile phase:** Acetonitrile and 0.02M potassium phosphate buffer (50: 50, v/v, pH 5) **Flowrate:** 1ml/min **Detection:** 235nm **Linearity Range:** 5-40µg/ml **Retention time:** 4.50 min **LOD:** 1.1µg/ml **LOQ:** 3.3µg/ml	[33]
5	Fluvastatin sodium in Bulk and its dosage form	RP-HPLC	**Stationary Phase:** Hypersil ODS C_{18} column **Mobile phase:** Methanol: 20mM Phosphate buffer (pH 3.0 adjusted with Phosphoric acid): acetonitrile (5:3: 2 v/v) **Flowrate:** 1.2ml/min **Detection:** 235nm **Linearity Range:** 1-6µg/ml **Retention time:** 7.65 min **LOD:** 0.0194µg/ml **LOQ:** 0.0588µg/ml	[34]
6	Fluvastatin sodium in bulk and Pharmaceutical dosage form	HPTLC	**Stationary Phase:** Silica gel 60 F_{254} **Mobile phase:** Methanol: Ethyl acetate: Toluene: Glacial acetic acid (3:5:1.8:0.2 v/v) **Detection:** 235 nm **Linearity Range:** 100-600ng/band **LOD:** 26.74ng/band **LOQ:** 81.05ng/band	[35]
7	Fluvastatin sodium in Bulk drug and dosage form	HPTLC	**Stationary Phase:** Silica gel 60 F_{254} **Mobile phase:** Chloroform: Toluene: Methanol (6:2:2) **Detection:** 305nm **Linearity Range:** 300-800ng/spot **LOD:** 65ng/spot **LOQ:** 200ng/spot	[36]

Table IV: Reported method of Fluvastatin in combination with other drugs.[37-39]

Sr. No	Drug	Method	Description	Ref No.
8	Fluvastatin and Fenofibrate in bulk drug and dosage form	UV Spectro-photometric	**Detection:** Fluvastatin-304nm Fenofibrate-288nm **Linearity Range:** Fluvastatin- 8-24µg/ml Fenofibrate- 2-16µg/ml **Correlation** **Co-efficient:** 0.999 **% Recovery:** 98%	[37]
9	Fluvastatin+ Valsartan	RP-HPLC	**Stationary Phase:** X-Terra C_{18} column **Mobile phase:** Acetonitrile: Potassium dihydrogen ortho phosphate buffer (pH 5, 60:40 v/v) **Flowrate:** 0.7ml/min **Detection:**237 nm **Linearity Range:** Fluvastatin -20-60µg/ml Valsartan-40-120µg/ml **Retention time:** Fluvastatin- 2.5 min Valsartan- 3.5 min **LOD:** Fluvastatin-3.01µg/ml Valsartan-2.99µg/ml **LOQ:** Fluvastatin-10µg/ml Valsartan-9.99µg/ml	[38]
10	Pravastatin+ Fluvastatin+ Atorvastatin +Rosuvastatin	Stability Indicating RP-HPLC	**Stationary Phase:** C_{18} column **Mobile phase:** Methanol–Water (60:40 v/v) and (70:30 v/v) **Flowrate:** 1ml/min **Correlation** **Co-efficient:** 0.999 **LOD:** Pravastatin-1.22 µg/ml Fluvastatin-2.02 µg/ml Atorvastatin-0.44µg/ml Rosuvastatin-1.55 µg/ml **LOQ:** Pravastatin-3.08 µg/ml Fluvastatin-6.12 µg/ml Atorvastatin -1.34 µg/ml Rosuvastatin -4.70 µg/ml	[39]

CONCLUSION

This review depicts the reported Spectroscopic and Chromatographic methods developed and validated for estimation of Ezetimibe and Fluvastatin. According to this review it was concluded that for Ezetimibe and Fluvastatin different Spectroscopic and Chromatographic methods are available for single and combination. The mobile phase containing Acetonitrile, Methanol, and Phosphate buffer were common for most of the chromatographic method to provide more resolution. For chromatographic method flow rate is observed in the range 0.6.-1.5 ml/min to get good resolution time. For most of the Spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

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