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AN OVERVIEW OF ANALYTICAL METHODS FOR DETERMINING SIMVASTATIN AND EZETIMIBE IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Ezetimibe is an anticholesteremic drug that binds to the brush border of the small intestine and inhibits cholesterol absorption, resulting in a reduction in cholesterol transport to the liver. Simvastatin is a prodrug in which the lactone ring is hydrolyzed in vivo to produce beta,delta-dihydroxy acid, an active metabolite. Simvastatin competes with HMG-COA for HMG-COA reductase after hydrolysis. UV-visible spectroscopy, HPLC (High Performance Liquid Chromatography), and HPLC (High Performance Liquid Chromatography) are the most regularly used methods for determining Simvastatin and Ezetimibe.

KEYWORDS: Simvastatin, Ezetimibe, RP-HPLC, RP-UPLC, HPTLC, UV-spectroscopy, Anticholesteremic.

INTRODUCTION

Butanoic acid, 2, 2-dimethyl-1, 2, 3, 7, 8, 8a-hexahydro-3, 7-dimethyl-8- [2 (tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl) -ethyl] Simvastatin (SIM) butanoic acid, 2, 2-dimethyl-1, 2, 3, 7, 8, 8a-hexahydro-3, 7-dimethyl-8--1-naphthalenyl ester is a lipid-lowering substance produced synthetically from Aspergillus terreus fermentation products. SIM, an inert lactone, is hydrolyzed to the equivalent -hydroxy acid, which inhibits 3-hydroxy 3-methyl glutaryl – coenzyme A. (HMG- CoA) reductase after oral administration. The conversion of HMG CoA to mevalonate, which is an early and rate-limiting step in cholesterol biosynthesis, is catalysed by this enzyme.

Simvastatin has the empirical formula C25H38O5 and a molecular weight of 418.574 g•mol1.

Figure 1 depicts the chemical structure.

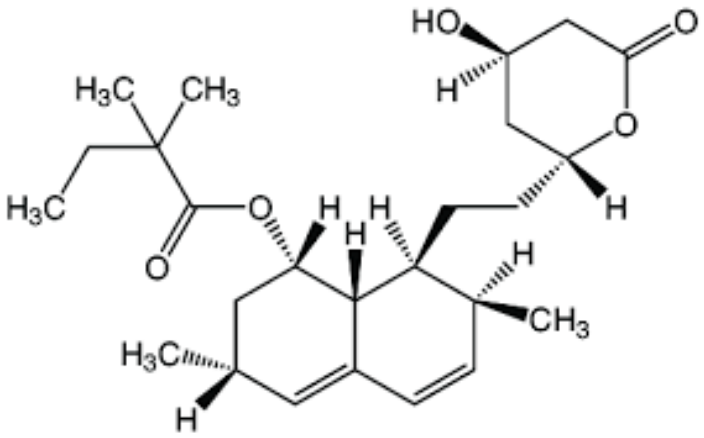

Figure 1: Simvastatin Structure.

1- (4-fluorophenly) – 3 (R)- [3-(4-fluorophenyl)- 3 (S) hydroxy propyl] Ezetimibe (EZ) -4 (S)–(4-hydroxy phenyl) – 2 azetidinones is a therapeutically useful medication that inhibits protein transporters on the small intestine brush border, resulting in active cholesterol transport. It also prevents the absorption of phytosterols3.

Ezetimibe has the empirical formula C24H21F2NO3 and a molecular weight of 409.433 g•mol1.

Figure 2 depicts the chemical structure.

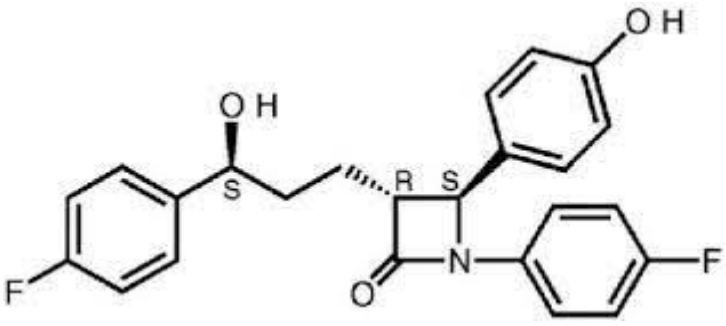

Figure 2: Ezetimibe's Structure.

EZE, unlike statins, has no effect on the absorption of lipid-soluble vitamins, triglycerides, or bile acids. When combined with statins, which limit cholesterol synthesis in the liver, this unique method of action has a synergistic cholesterol-lowering impact.

The following factors are taken into account when categorising reported methods

1. UV-Spectroscopy, chromatography, and other procedures for determining Simvastatin alone and in combination with other medications.
2. UV spectroscopy, chromatography, and other procedures for determining Ezetimibe alone and in combination with other medications.
3. UV spectroscopy, chromatography, and other techniques for determining Simvastatin coupled with Ezetimibe.

Table 1: UV-Spectroscopy, chromatography, and other procedures for determining Simvastatin alone and in combination with other medicines.

Sr.no	Drugs	Method	Description	Ref .no
1.	**Simvastatin In bulk and tablet dosage form**	**HPLC**	**Detection wavelength –** 239nm **Column –** Waters C8, 5µm, 15cmx4.5mm i.d. **Mobile phase –** ACN: phosphate buffer(pH 3)= 8:2 **Flow rate –** 1.2 ml/minute **Retention time –** 4.975 min **Total run time –** 10 min **Linearity range –** 10-100 µg/ml **Regression coefficient –**0.995	[8]
2.	**Simvastatin In Bulk and Tablet Dosage Form**	**UV-Visible Spectroscopy**	**Detection wavelength –** 238nm **Solvent –** ethanol & Water **Linearity range –** 2 to 50 µg/ml **Regression coefficient -** 0.9992 **% Recovery –** 99.84% **LOD –**0.15µg/ml **LOQ –** 2.37µg/ml	[9]
3.	**Simvastatin In Bulk and Tablet Dosage Form**	**RP-HPLC**	**Detection wavelength –** 236nm **Column –** Develosil ODS HG5 RP C18, 5µm, 150cmx4.6mm **Mobile phase –** ACN: phosphate buffer(pH 3)= 85:15v/v **Flow rate –** 1.0 ml/minute **Retention time –** 5.84 min **Total run time –** 10 min **Linearity range –** 10-100µg/ml **Regression coefficient –**0.999 **LOD –** 0.341 **LOQ –** 1.023	[10]
4.	**Simvastatin and Sitagliptin in Tablet dosage form**	**RP-HPLC**	**Detection wavelength –** 253nm **Column –** intersil ODS -3 C18(75 mm*4.6 mm) 5µ **Mobile phase –** 0.05 M	[13]

			Ammonium acetate:ACN(60:40%v/v) **Flow rate –** 1.0ml/minute **Retention time –** SIM – 3.260 min SIT – 2.136 min **Total run time –** 12 min **Linearity range –** SIM – 25-150µg/ml SIT – 10-60µg/ml **Regression coefficient –** SIM – 1.0 SIT –1.0	
5.	**Simvastatin in Bulk drug**	**RP-HPLC**	**Detection wavelength –** 240nm **Column –** Symmetry ODS-3V(5µm, 150cmx4.6mm i.d.) **Mobile phase –** ACN: 0.02M buffer(pH 3.5)= 60:40%v/v **Flow rate –** 1.2 ml/minute **Retention time –** 12.033 min **Total run time –** 10 min **Linearity range –** 1-150 µg/ml **Regression coefficient –**0.999 **Tailing factor –** 1.12	[14]
6.	**Simvastatin in Bulk and Pharmaceutical Dosage forms**	**RP-HPLC**	**Detection wavelength –** 238nm **Column –** Agilent ODS UG C18 (5µm, 250cmx4.5mm i.d.) **Mobile phase –** ACN: Methanol: Phosphate buffer(pH 3.0)= 50:40:10%v/v **Flow rate –** 1.0ml/minute **Retention time –** 4.3 min **Total run time –** 10 min **Linearity range –** 5-25 µg/ml **Regression coefficient –**0.999 **Tailing factor –** 0.45 **LOD –**0.21 µg/ml **LOQ –** 0.63µg/ml	[15]
7.	**Simvastatin**	**UV Spectroscopy**	**Detection wavelength –** 233nm **Solvent –** Phosphate buffer(pH-6.8) **Linearity range –** 0.01to 0.08 µg/ml **Regression coefficient -** 0.999 **% Recovery –** 98.88%	[17]
8.	**Simvastatin and Labetalol**	**UV Spectroscopy**	**Detection wavelength –** **SIM-** 239nm **LAB -**222.4 nm	[19]

			Solvent – 0.25N NAOH **Linearity range –** **SIM-** 2-10 µg/ml **LAB -**2-10 µg/ml 0.01to 0.08 µg/ml **Regression coefficient –** **SIM-** 0.991 **LAB -0.997** **% Recovery-** **SIM-** 98.3% **LAB -** 98.2%	

Table 2: UV-Spectroscopy, chromatography, and other procedures for determining Ezetimibe alone and in combination with other medications.

1.	**Ezetimibe in Bulk and Dosage Forms**	**RP-HPLC**	**Detection wavelength –** 233.5nm **Column –** Phenomenex RP C18, 5µm, 250cmx4.6mm **Mobile phase –** ACN: Water= 42:58v/v **Flow rate –** 1.2ml/minute **Retention time –** 3.5 min **Total run time –** 10 min **Linearity range –** 10-50µg/ml **Regression coefficient –**0.999	[21]
2.	**Ezetimibe and Rosuvastatin in Combined Tablet Dosage Form**	**RP-HPLC**	**Detection wavelength –** 230nm **Column –** Sunfire BDS C18, 5µm, 250cmx4.6mm **Mobile phase** – Ammonium acetate :ACN (55:45%v/v) **Flow rate –** 0.8ml/minute **Retention time –** **RVS-** 2.74min **EZE-** 4.80 min **Total run time –** 10 min **Linearity range –** **RVS-** 98.19-294.56µg/ml **EZE** -99.12-297.36 µg/ml **Regression coefficient –** **RVS**-0.999 **EZE** -0.999 **Tailing Factor-** 1.0 **LOD –** **RVS**-3.3µg/ml **EZE**-3.7 µg/ml **LOQ** – **RVS-** 10.0µg/ml **EZE**-11.24µg/ml	[22]
3.	**Ezetimibe in Tablet**	**HPLC**	**Detection wavelength –** 240nm	[23]

			Column – Perfectsil 5µm, 250cmx4.6mm **Mobile phase –** ACN: Ammonium acetate 10mM (75:25%v/v) **Flow rate –** 1.0ml/minute **Retention time –** 3.5 min **Total run time –** 10 min **Linearity range –** 10-60µg/ml **Regression coefficient** –0.996	
4.	**Ezetimibe and Rosuvastatin Calcium in Pharmaceutical dosage forms**	**RP-HPLC**	**Detection wavelength –** 252nm **Column –** C18G, 5µm, 250cmx4.6mm **Mobile phase** – ACN :Water (75:25%v/v) **Flow rate –** 0.6ml/minute **Retention time –** **RVS-** 2.9min **EZE-** 6.5 min **Total run time –** 8 min **Linearity range –** **RVS-** 5-40µg/ml **EZE** -5-40µg/ml **Regression coefficient –** **RVS**-0.9995 **EZE** -0.9992 **Tailing Factor-** **RVS**-1.3 **EZE-1.2** **LOD –** **RVS**-0.76µg/ml **EZE-**0.91 µg/ml **LOQ** – **RVS-** 2.3µg/ml **EZE-**2.7µg/ml	[24]
5.	**Ezetimibe in Tablet Dosage Form**	**RP-HPLC**	**Detection wavelength –** 230nm **Column –** ODS 3V C18, 5µm, 250cmx4.6mm **Mobile phase –Ammonium acetate buffer:** ACN: Water= 45:55%v/v **Flow rate –** 1.5ml/minute **Retention time –** 9.88 min **Total run time –** 25 min **Linearity range –** 10-50µg/ml **Regression coefficient** –0.999	[27]

Table 3: UV spectroscopy, chromatography, and other procedures for determining Simvastatin coupled with Ezetimibe.

Sr.no.	Drugs	Method	Description	Ref.no.
1.	**Simvastatin and ezetimibe In Bulk and Pharmaceutical Formulations**	**Stability indicating HPLC**	**Detection wavelength –** 225nm **Column –** Sunfire C18column(250mm x 4.60mm,5µ) **Mobile phase –** ACN: Potassium Dihydrogen Phosphate (pH 7.2)= 60:40v/v **Flow rate –** 1.8 ml/minute **Retention time –** SIM – 2.35 min EZE – 7.23 min **Total run time –** 10 min **Linearity range –** SIM -50-150µg/ml EZE-50-150 µg/ml **Regression coefficient –** SIM – 0.999 EZE – 0.999 **LOD –** SIM –0.61µg/ml EZE – 0.29µg/ml **LOQ –** SIM – 2.01µg/ml EZE – 0.97µg/ml **Tailing Factor –** SIM – 1.0 EZE – 1.3	[11]
2.	**Simvastatin and Ezetimibe In Pharmaceutical Formulations**	**HPLC**	**Detection wavelength –** 240nm **Column –**Merck C-18 250*4.6, i.d., 5 µ **Mobile phase –** 0.1M ammonium acetate buffer pH 5.0 :CAN 30:70v/v **Flow rate –** 1.5 ml/minute **Retention time –** SIM – 9.80 min EZE – 2.95 min **Total run time –** 10 min **Linearity range –** SIM -20-60µg/ml EZE-20-60µg/ml **Regression coefficient –** SIM – 0.9992 EZE – 0.9996 **LOQ –** SIM – 0.17µg/ml EZE – 0.19µg/ml	[12]

3.	**Simvastatin and ezetimibe in tablet dosage form**	**RP-HPLC**	**Detection wavelength –** 240nm **Column –**Symmetry C8 (4.6mm x 150mm, 5µm) **Mobile phase –** ortho phosphoric acid buffer and Acetonitrile,40:60V/V **Flow rate –** 1.5 ml/minute **Retention time –** SIM – 9.80 min EZE – 2.95 min **Total run time –** 10 min **Linearity range –** SIM -20-60µg/ml EZE-20-60µg/ml **Regression coefficient –** SIM – 0.9992 EZE – 0.9996 **LOQ –** SIM – 0.17µg/ml EZE – 0.19µg/ml	
4.	**Simvastatin and Ezetimibe in Bulk and Dosage Forms**	**RP-HPLC**	**Detection wavelength –** 248nm **Column –**Symmetry C8 (4.6mm x 25mm, 5µm) **Mobile phase –** Methanol:Water 95:05%V/V **Flow rate –** 0.8 ml/minute **Retention time –** SIM – 4.9min EZE – 3.2 min **Total run time –** 10 min **Linearity range –** SIM -5-50µg/ml EZE-5-70µg/ml **Regression coefficient –** SIM – 0.9996 EZE – 0.9995 **LOQ –** SIM – 0.04µg/ml EZE – 0.04µg/ml **Tailing factor –** SIM – 1.01 EZE – 1.03	**[16]**
5.	**Simvastatin and Ezetimibe in Bulk and Pharmaceutical Dosage Forms**	**UV Spectrophotometry**	**Detection wavelength –** **SIM-** 248 **EZE-** 244nm **Solvent –** 0.1N NAOH **Linearity range –** **EZE -** 0.5-30 µg/ml **SIM -** 1.0 to 40 µg/ml **Regression coefficient -** 0.9992	**[18]**

			% Recovery – **EZE** -99.6% **SIM**-98.9%	
6.	**Simvastatin and Ezetimibe in Pharmaceutical Formulations**	**RP-HPLC**	**Detection wavelength –** 236nm **Column –**X-terra RP18 C18column(50mm x 4.6mm,5µ) **Mobile phase –** ACN: Phosphate buffer(pH 3.0)= 55:45v/v **Flow rate –** 0.8 ml/minute **Retention time –** SIM – 3.3 min EZE – 0.8 min **Total run time –** 10 min **Linearity range –** SIM -40-120µg/ml EZE-5-15 µg/ml **Regression coefficient –** SIM – 0.999 EZE – 0.999 **Tailing Factor –** SIM – 1.1 EZE – 1.2	**[20]**
7.	**Simvastatin and Ezetimibe in combined dosage forms**	**UV spectroscopy**	**Detection wavelength –** **SIM-** 238.4nm **EZE-** 228.8nm **Solvent –** ACN **Linearity range –** **EZE –** 2-18 µg/ml **SIM –** 2-18µg/ml **Regression coefficient** - 0.9999 **% Recovery –** **EZE** -100-101% **SIM**-100-107% **LOD-** SIM – 0.26µg/ml EZE – 0.33µg/ml **LOQ –** SIM – 1.0µg/ml EZE – 0.806µg/ml	**[25]**
8.	**Simvastatin and Ezetimibe**	**HPTLC**	**Detection wavelength –** 250nm **Column –**Perforated Silica gel 60F **Mobile phase –** Chloroform:Benzene:Methanol:acetic acid(6:3:1:0.1) **Retention time –** SIM – 9.80 min EZE – 2.95 min **Total run time –** 10 min **Linearity range –**	**[26]**

			SIM -0.8-4.0µg/spot EZE-0.1-1.0µg/spot **Regression coefficient –** SIM – 0.9992 EZE – 0.9995 **LOD –** SIM – 170 ng/spot EZE – 20 ng/spot **LOQ –** SIM – 570 ng/spot EZE – 70 ng/spot	

CONCLUSION

The study summarises the reported spectroscopic and chromatographic methods for estimating Simvastatin and Ezetimibe in bulk and pharmaceutical dosage forms that have been developed and validated. In this investigation, it was discovered that multiple spectroscopic and chromatographic approaches are available for Simvastatin and ezetimibe, both alone and in combination with other medicines. These approaches are said to be simple, accurate, cost-effective, precise, and repeatable. RP-HPLC and UV absorbance detection were used in the majority of these procedures.

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