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UV SPECTROPHOTOMETRIC METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF SIMVASTATIN IN BULK AND TABLET DOSAGE FORM USING MIXED HYDROTROPY SOLUBILISATION TECHNIQUE

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ABSTRACT

Simple and cost-effective UV spectrophotometric method for estimation of Simvastatin (SMV) in bulk and tablet dosage form have been developed using mixed hydrotropic technique by absorbance maxima and area under the curve (AUC) method and validated as per ICH guidelines. In present study, 2 M urea, 1 M sodium acetate and 1 M sodium citrate (20:40:40 % v/v/v) solution used as mixed hydrotropic solution to enhance aqueous solubility of poorly water soluble drug Simvastatin. Method A involved absorbance maxima method which based on the measurement of absorbance at λmax of Simvastatin 238 nm while method B involved area under the curve method based on the measurement of AUC in the range of 234-240 nm. Urea solution does not interfere in the absorption of drug. Proposed method was validated as per ICH guidelines in terms of accuracy, linearity, precision, LOD and LOQ. Proposed method found to be linear in concentration rangeof 8-48 µg/ml for SMV.The results of validation parameters also indicated that proposed method was found to be accurate, precise, reproducible, sensitive and suitable for routine quality control analysis for estimation of Simvastatin in bulk and Tablet dosage form.

Key Words: Absorbance maxima method, Simvastatin (SMV), Area under the curve (AUC) and ICH guidelines.

INTRODUCTION

Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water soluble drugs. Hydrotropic solubilisation is one of them. The term "hydrotropy" has been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. Sodium benzoate, sodium salicylate, niacinamide, sodium hydroxide and urea have been employed to enhance the aqueous solubility of poorly water-soluble drugs.[1] So far,many UV spectrophotometric methods involving the solubility enhancement of various poorly water soluble drugs using hydrotropic solubilisation phenomenon viz Furosemide[2],Ketoprofen & Salicylic acid[3]Cefixime[4], Tinidazole[5]Amoxicillin[6] Accelofenac[7]and Hydrochlorothiazide[8]have been developed.

Simvastatin belongs to a class of drugs called HMG-CoA reductase inhibitors commonly called statins that derived synthetically from fermentation products of Aspergillus terreus. All statins act by inhibiting 3-hydroxy-3-methylglutarylcoenzyme (HMG-CoA).A HMG-CoA reductase, the rate limiting enzyme of the HMG-CoA reductase pathway, the metabolicpath way responsible for the endogenous production of cholesterol mainly used for the treatment of dyslipidaemia and the prevention of cardiovascular diseases[9].

Simvastatin is prodrug which is converted into its β- hydroxy which inhibits HMG CoA reductase(3-hydroxy-3-methyl glutarylCoenzyme A) enzyme, responsible for catalysing the conversion of HMG CoA to mevalonate a rate limiting step in the synthesis of cholesterol in liver[10]. It is chemically known as(1S, 3R, 7S, 8S, 8aR)-8-{2-[(2r, 4r)-4-hydroxy-6-oxotetrahydro-2H-pyran-2yl]-ethyl}-3, 7-dimethyl-1, 2, 3, 7, 8.8a hexahydronapthalen-1-yl-2, 2-dimethylbutanoate (Fig.1). Simvastatin can be estimated by UV spectrophotometry[11-29]UPLC[30], RP-HPLC[27-29, 30-44], HPTLC[45-49]and LC-MS/MS[50] alone or in combination with other drugs.

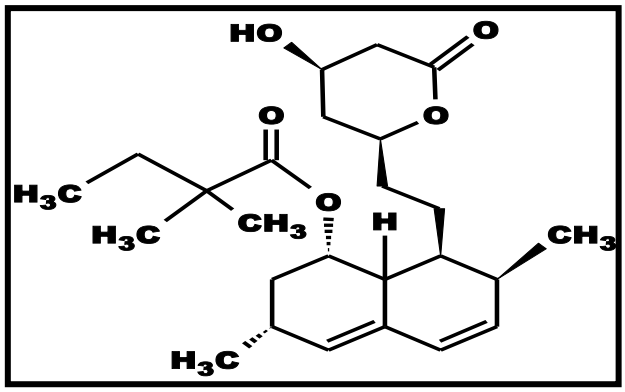

Fig.1.Chemical structure of Simvastatin

Literature survey reveals that so far, there were so many UV spectrophotometric methods have been reported but except[15, 16&17] no one tried to increase the aqueous solubility of Simvastatin using mixed Hydrotropy as one of the solubilisation technique for the estimation of Simvastatin.. Therefore main aim of present study was that to develop simple and economic UV spectrophotometric method for the estimation of Simvastatin in bulk and tabletdosage form using Hydrotropy technique and validate the same as per ICH guidelines[51].

MATERIALS AND METHODS

Chemicals and reagents

The pure API sample of Simvastatin was obtained as free gift sample from Gen Pharma International Pvt. Ltd; Pune(India) while all spectroscopy grade solvent such as methanol and AR grade urea, sodium acetate and sodium citrate were purchased from E. Merck Private Ltd; India and double distilled water was used for whole experiment. The marketed pharmaceutical tablet dosage form of Simvastatin i.e. Simvas 10 (Micro Labs India Pvt. Ltd.) was purchased from local market.

Instrumentation

A Jasco double beam UV–visible spectrophotometer, Model: V-630, with a fixed bandwidth (2nm) and 1-cm quartz cell was used for Spectral and absorbance measurements.

Preliminary solubility studies of drug

Solubility of Simvastatin was determined at 27 ±1°C. An excess amount of drug was added to screw capped 30 ml glass vials each containing different aqueous system viz. distilled water, buffer of different pH (8 8.5 and 9), 2 M Urea, 1 M sodium acetate solution, 1M sodium citrate and 1 M sodium salicylate. The vials were shaken for 12 hrs at 27±1°C in a mechanical shaker. These solutions were allowed to equilibrate for the next 12 hours and then centrifuged for 20 minutes at 2000 rpm. The supernatant of each vial was filtered through Whatmann filter paper No.41. The filtrates were diluted suitably and analysed spectrophotometrically against corresponding

solvent blankwithin UV range of 200-400 nm.

Preparation of standard stock solution of Simvastatin

Transfer 2.5 mg of pure simvastatin in 25 ml of volumetric flask containing 10 ml mixture of 5 M urea, 1 M sodium acetate and 1 M sodium citrate (20:40:40 % v/v) as mixed hydrotropic solubilizing agentthen sonicated and for 15 minutes and final volume made upto mark with distilled water and solutions were then filtered through Whatmann filter paper No.41 to form 100µg/ml std. stock solution ofSimvastatin.

Preparation of calibration curve of Simvastatin

From above std. stock solution, pippete out aliquots of 0.8 to 4.8 ml and transferred to series of 10 ml volumetric flasks containingdistilled water then sonicated for 15 minutes and final volume made upto mark with distilled water and solutions were then filtered 41 to form solutions of 8 to 48 µg/ml. These solutions were then scanned in the range of 200-400 nm against blank. The absorbance maxima was found to be 238 nm and then calibration curve was plotted as absorbance vs. concentration.

Sample preparation for tablet assay of Simvastatin

Twenty tablets (Simvas) containing 10 mg of Simvastatin weighed, average weight calculated and triturated to fine powder and then weight equivalent to 10 mg of Simvastatin transferred to 100 ml of volumetric flask containing mixture of 2 M urea, 1 M sodium acetate and sodium citrate (20:40:40 % v/v) as mixed hydrotropic solubilizing agent, then sonicated for 15 minutes and final volume made upto mark with distilled water and filtered through Whatman filter paper no. 41 to form 100 µg/ml stock solution. From this, 1 ml of aliquot transferred in 10 ml of volumetric flask containing distilled water to form 10 µg/ml solution and scanned in the range of 200-400 nm against distilled water asblank at 238 nm. The drug content of solution was calculated by using standard calibration curve.

Absorption maxima method

For the selection of analytical wavelength, 10 µg/ml solution of Simvastatin was scanned in the spectrum mode from 200 nm to 400 nm separately. From the spectra of drug, λmax of SMV, 238 nm was selected for the analysis (Fig. 2). Dilutions of standard stock solution (100 µg/ml) were made and calibration curve was plotted.

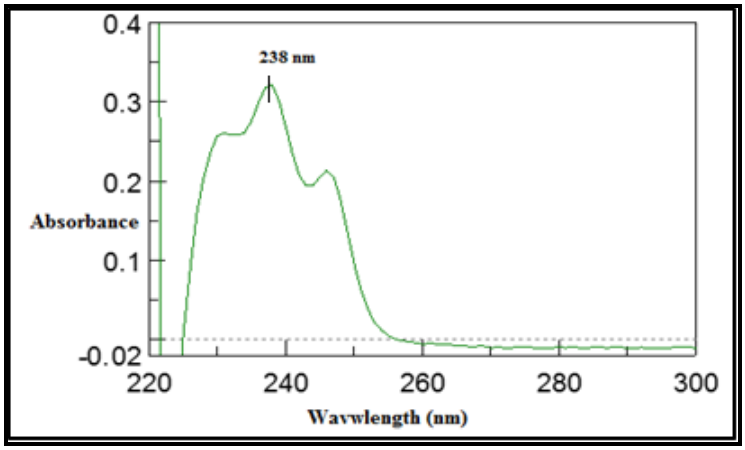

Fig.2.Absorption maxima of Simvastatin

Area under curve method

For the determination of Simvastatin using the area under curve (AUC) method, suitable dilutions of the std. stock solution (100 µg/ml) of Simvastatin were prepared and scanned in the range of 200 - 400 nm. For Area under curve method, the sampling wavelength ranges from 234-240 nm.(Fig. 3) selected for estimation of Simvastatin and area were integrated between these selected wavelength range, which showed linear response with increasing concentration hence the same wavelength range were used for estimation of tablet formulations.

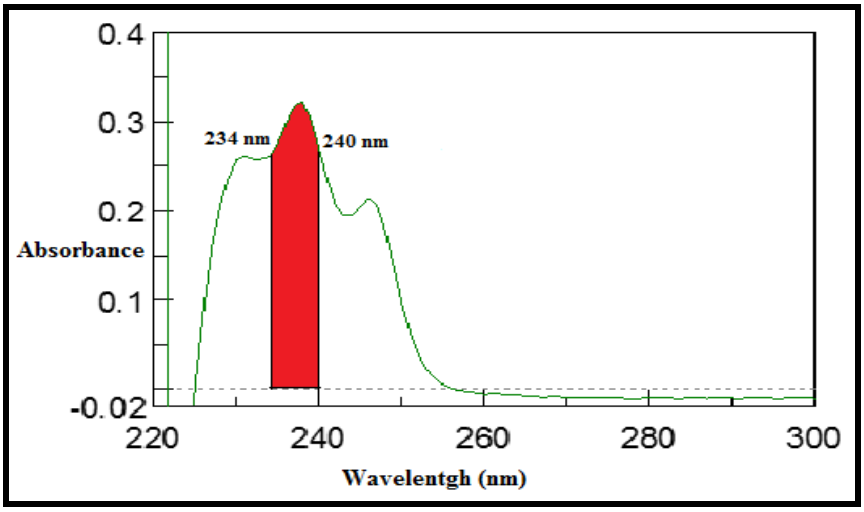

Fig.3.Area under the Curve Method

VALIDATION

The present UV spectrophotometric methods were validated for linearity, precision, accuracy, LOD and LOQ as per ICH guidelines for estimation of Simvastatin in bulk and tablet dosage form.

Linearity

From std. stock solutions of Simvastatin (100 µg/ml), pippete out aliquots of 0.8 to 4.8 ml of Simvastatin transferred to series of 10 ml volumetric flasks and final volume made upto mark with methanol as diluent to form solutions of 8 to 48 µg/ml of Simvastatin. These solutions were then scanned in the range of 200-400 nm against diluent as blank and then calibration curve was plotted as absorbance vs. concentration to check the linear relationship between absorbance and concentration of Simvastatin

Precision

Precision study expressed by carrying out Repeatability (intraday precision) and interday precision. The intraday (Repeatability) and interday precision study were carried out by estimating corresponding responses three times on the same day and on the three different days for the three different concentration for (8, 16 and 24 µg/ml) for Simvastatin. The results of precision study were reported in terms of % relative standard deviation

Accuracy

The accuracy of developed method was carried out by calculating the % recovery of Simvastatin by standard addition method at three different levels i.e. 80 %, 100 % and 120 %. Known amount of standard solutions of SMV (14.4, 16 and 17.6 µg/ml) were added to prequantitated sample solutions of 16 µg/ml of SMV).

LOD and LOQ

Limit of detection (LOD) is defined as lowest concentration of analyte that can be detected while limit of quantitation is defined as lowest concentration of analyte that can be quantitated. With suitable precision and linearity. LOD and LOQ can be calculated from the following formulas

LOD = 3.3* r / S & LOQ = 10 * r/ S

Where r is the Standard deviation of y-intercept of the regression line and S is slope of the calibration curve.

RESULTS AND DISCUSSION

Method development and optimization

The present paper describes application of hydrotropic solubilisation technique for the estimation of Simvastatin (SMV) in bulk and tablet dosage form by Absorbance maxima method and area under the curve. Solubility studies indicated that aqueous solubility of Simvastatin was enhanced in optimized mixed hydrotropic mixture i.e. 2 M urea, 1 M sodium acetate and 1 M sodium citrate (20:40:40 % v/v/v) as compared to solubility in other economic solvents such as distilled water. Even Simvastatin remained stable in optimized hydrotropic solvent mixture for 36 hours in stability studies. Hydrotropic solvent mixturedoes not interfere in the absorption of Simvastatin (λmax-238 nm).The pH of present mixed hydrotropic mixture solution was 8-9 therefore, in order to study the influence of

increased pH on the solubility of Simvastatin, the solubility of Simvastatin was also checked in buffer solution of pH 8-9 but there was no significant effect on solubility of Simvastatin found. This proved the increased solubility of Simvastatin in hydrotropic solution was not due to alteration in pH but due to only hydrotropic effect of present hydrotropic mixture.

Organic solvents like methanol, chloroform, ethanol, dimethyl formamide, benzene, hexane, acetone, toluene, carbon tetrachloride, diethyl ether and acetonitrile are widely used in spectrophotometric estimations of poorly water-soluble drugs. Most of these organic solvents are toxic, costlier and are can be the sources of pollution. Inaccuracy in spectrophotometric estimations due to volatility of organic solvents is another drawback of these solvents. Hydrotropy method offers some advantages by excluding the usage of such costlier, toxic, volatile and volatile by incorporating the use of hydrotropic solvents. Therefore the present methods were found to be simple, economic and non-toxic.

Validation

Linearity

Linearity was evaluated by analysis of Std. SMV at Six different concentrations. SMV found to be linear within conc. range of 8-48 µg/ml with regression coefficient of 0.9998 by the method A and 0.991 by method B (Fig.4 & 5). The results of regression analysis are summarized in (Table 1). Results show that within the concentration range mentioned above, there was an excellent correlation between peak area and concentration.

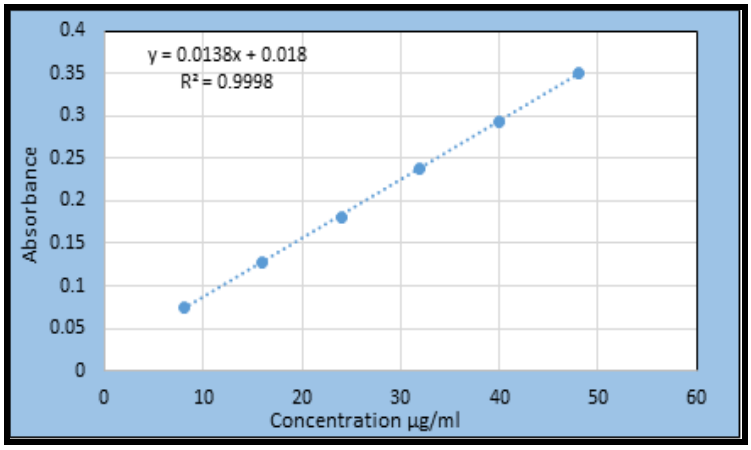

Fig.4.Linearity of Simvastatin by Method A

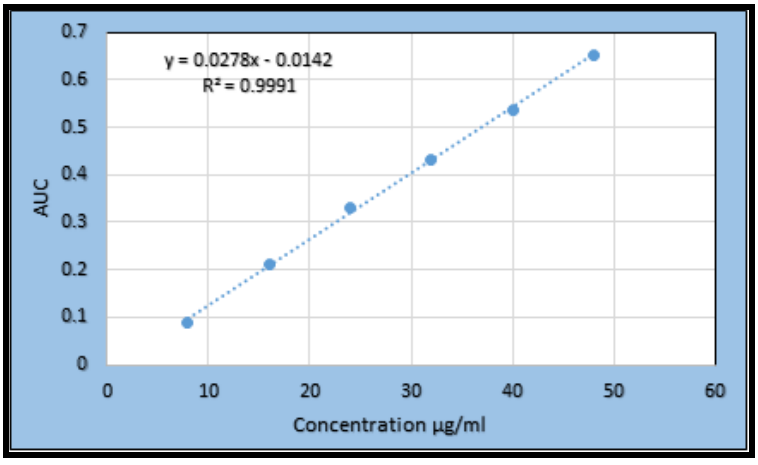

Fig.5.Linearity of Simvastatin by Method B

Table.1.Results of regression analysis of SMV

Simvastatin	Beer's Range (µg/ml)	Regression equation	Regression coefficient (r^2)
Method A	8-48	y = 0.0138x+0.018	0.9998
Method B	8-48	y = 0.0278x-0.0142	0.9991

Precision

The repeatability (intra-days precision) is expressed as percentage relative standard deviations (% RSD). The average % RSD values of intra-days precision for SMV at the concentrations of 8, 16 and 24µg/ml were 0.703,0.253 & 0.087 for method A while 0.044, 0.173 & 0.122µg/ml for method B and for inter-days precision, the average % RSD were 0.097, 0.050 and 0.049µg/ml respectively for method A while 0.098, 0.070 and 0.091µg/ml for method B respectively. The % RSD levels of intra-day and inter-day precision were less than 2 in all cases, which indicated that there were no significant variations in the analysis of SMV at the concentrations and the proposed methods were precise which are shown in (Table 2 & 3).

Table.2. Results of Intraday Precision Study

Simvastatin	Conc. taken (µg/ml)	Conc. found (µg/ml) *	%Amt. found	S.D.	% R.S.D.
Method A	8	7.84	98.15	0.690	0.703
	16	15.80	99.92	0.250	0.253
	24	23.68	99.68	0.086	0.087
Method B	8	7.91	98.87	0.044	0.044
	16	15.68	96.00	0.170	0.173
	24	23.86	99.41	0.122	0.122

***Average of three estimations, S.D. – Standard Deviation, R.S.D. - Relative Standard Deviation**

Table.3. Results of Interday Precision Study

Simvastatin	Conc. taken (µg/ml)	Conc. found * (µg/ml)	% Amt. found	S.D.	% R.S.D.
Method A	8	7.75	96.87	0.094	0.097
	16	15.46	96.62	0.048	0.050
	24	23.83	96.29	0.049	0.049
Method B	8	7.76	97.00	0.095	0.098
	16	15.93	99.56	0.069	0.070
	24	23.77	99.04	0.090	0.091

***Average of three estimations**

Accuracy (Recovery Study)

The accuracy was assessed by the standard addition method of three replicate determinations of three different solutions containing 14.4, 16 and 17.6 µg/ml of SMV. The average % recoveries for three different concentrations was found to be 98.37 for method A and 99.74for method B of SMV using proposed UV spectrophotometric methods. The higher values indicated that the proposed UV spectrophotometric methods were accurate for the determination of SMV in pharmaceutical dosage form. Results of recovery studies are summarized in (Table 4).

Table.4. Results of Recovery Studies

Drugs	Conc. of Drug taken (µg/ml)		% Recovery *
	From Tablet	From API	
Method A	16	14.4	98.71
	16	16	97.90
	16	17.6	98.52
Method B	16	14.4	98.56
	16	16	100.59
	16	17.6	100.08

***Average of three estimations**

LOD and LOQ

The limit of detection was found to be 0.87µg/ml and 0.84µg/ml for method A and for method B respectively. The limit of quantification was found to be 2.65µg/ml for method A and 6.23 µg/ml for method B respectively. Low values of LOD and LOQ indicates that the developed methods were sensitive for the estimation SMV in bulk and tablet dosage form. Results of LOD and LOQ are summarized in (Table 5).

Table.5. Results of LOD and LOQ

Drugs	LOD (µg/ml)	LOQ (ng/band)
Method A	0.87	2.65
Method B	0.84	6.23

Assay

Analysis of sample of marketed tablet containing 10 mg Simvastatin was carried out and the amounts recovered were expressed as a percentage amount of the label claims. The percentage recovery of Simvastatin were 99.15 for method A and 99.52 for method B

Respectively and these values are complying with the assay specifications for active drug Simvastatin in the United States of Pharmacopoeia (90.0–110.0%) which are required to be met by most drug formulations. Results of tablet assay are summarized in (Table 6).

Table.6. Results of Tablet Assay

Simvastatin	Label Claim (mg/tab)	Amount of Drug* Estimated (mg/tab)	% Assay
Method A	10 mg	9.81	98.15
Method B	10 mg	9.85	98.52

***Average of Six estimations**

CONCLUSION

Simple, economic, fast and non-toxic UV spectrophotometric methods have been developed for the estimation of Simvastatin in bulk and tablet dosage form by absorbance maxima and area under the curve method using mixed hydrotropic as solubilisation technique. Hydrotropy method excludes the usage of costlier, toxic and volatile organic solvents by using economic and non-toxic hydrotropic solvents. Here hydrotropic solvent mixture 2M urea, 1 M sodium acetate and 1M sodium salicylate (20:40:40 % v/v/v) enhanced the aqueous solubility of Simvastatin. The methods also validated as per ICH guidelines for linearity, precision, accuracy, LOD and LOQ. The results of these parameters also indicated that the present UV spectrophotometric methods were found to be linear, precise, accurate and sensitive and can be used for routine quality control analysis of Simvastatin in bulk and tablet dosage form.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

REFERENCES

1. Maheshwari RK, Rajput MS, Sinha S.New quantitative estimation of benzoic acid bulk sample using calcium disodium edetate as hydrotropic solubilizing agent Asian J Pharma and Clin Res 2010 Feb 3(1): 43-45.
2. Maheshwari RK, Chaturvedi SC, Jain NK. Application of hydrotropic solubilisation phenomenon in spectrophotometric

determination of pharmaceutical dosage forms, Indian Drugs2005 May 42: 760-3.
3. Maheshwari RK. Novel spectrophotometric estimation of Cefixime in tablets using hydrotropic solubilisation phenomenon. Asian J of Chem 2006 Jan 18: 393-6.
4. Maheshwari RK.A novel application of hydrotropic solubilisation in the analysis of bulk samples of Ketoprofen and Salicylic acid. Asian J of Chem 2006 Aug 18:194-6.
5. Maheshwari RK. Novel application of hydrotropic solubilisation in the spectrophotometric analysis of Tinidazole in dosage form.Asian J chem. 2006 Aug 18: 640-6.
6. Maheshwari RK. Spectrophotometric analysis of Amoxicillin in tablets using hydrotropic solubilisation technique. Asian J Chem 2006Aug 18: 194-6.
7. Maheshwari RK, Chaturvedi SC, Jain NK. Application of hydrotropic solubilisation phenomenon in spectrophotometric determination of pharmaceutical dosage forms. Indian drugs. 2005 Mar 42: 760-3.
8. Maheshwari RK Chaturvedi SC, Jain NK. Application of hydrotropic solubilisation phenomenon in spectrophotometric analysis of hydrochlorothiazide tablets.Indian drugs 2005 Sep 42: 541-4.
9. Maryadele JO. Merck Index. USA; Neil Edu;2001.
10. Bays HE, Moore PB, Drehobl MA. Effectiveness and tolerability of simvastatin in patients with primary hypercholesterolemia pooled analysis of two phase II studies Cli Ther 2001 Jan 23(8): 1209-1230.
11. Arayne MS, Sultana N, Hussain F & Ali SA. Validated spectrophotometric method for quantitative determination of simvastatin in pharmaceutical formulations and human serumJournal of Analytical Chemistry. 2007 Jun 62(6): 536-541.
12. Jain N, Jain R, Swami H, Pandey S & Jain DK.Internat.RP-HPLC Method for Simultaneous Estimation of Simvastatin and Ezetimibe in Bulk Drug and its Combined Dosage Form. J Pharma Pharma Sci2009 Jan 1(1): 170-175.
13. Rajput SJ & Raj HA.Simultaneous spectrophotometric estimation of Ezetimibe and Simvastatin in tablet dosage forms.Indian J of Pharma Sci.2007 Jul 69(6): 759.
14. Balaji S & Sunitha A. Development and validation of spectrophotometric method for simultaneous determination of Simvastatin and Ezetimibe in tablet formulationsPak J Pharma Sci2010 Apr *23*(4): 375-378.
15. Sable PN, Challenge GM, Bhosale AV.Novel spectrophotometric estimation of Izetemib, Losorton and Simvastatin using hydrotropic solubilizing agents.Inter J of ChemTech Res 2009 May 1(4): 1393-1397.
16. Patil DN. New application of hydrotropic solubilization phenomenon in spectroscopic estimation of simvastatin in tablet dosage form J Chem Pharma Res 2012 Oct 4(10): 583-585.
17. Sharma S, Sharma MC, Sharma R, Sharma AD. Simultaneous Estimation and Validation of Ezetimibe and Simvastatin in Combined Tablet Dosage Forms by Hydrotropic Solubilization Technique Using 3.0 M Urea.J of Pharma Res 2010 May 3(5): 1063-1067.
18. Mane VB, Babar S. & Kulkarni N. Development of UV Spectrophotometric method for the simultaneous estimation of Simvastatin and Ezetimibe in tablet dosage form by simultaneous Equation and Absorbance ratio method. Inter J of ChemTech Res 2011 Mar 3(3):1459-1466.
19. Bhatia NM, Deshmukh DD, Kokil SU, Bhatia MS. Simultaneous spectrophotometric estimation of Simvastatin and Ezetimibe in tablet formulation.J Chem2009 Feb 6(2): 541-544.
20. Singla V, Bhaskar R& Bhaskar R. Simultaneous Estimation of Simvastatin and Metformin Hydrochloride in Bulk and Solid Dosage Forms.Rasayan Journal2010 Oct 3(3): 507-513
21. Palabiyik IM., Onur F, Yardimci C, Ozaltin N.Simultaneous spectrophotometric determination of Ezetimibe and Simvastatin in pharmaceutical preparations using chemometric techniquesQuímica Nova 2008 May3(5): 1121-1124.
22. Thamake SL, Jadhav SD, Pishawikar SA. Development and validation of method for simultaneous estimation of Atorvastatin Calcium and Ramipril from capsule dosage form by first order derivative spectroscopy.Asian J. Res Chem 2009 Jan 2(1): 52-53.
23. Moussa BA, Mohamed MF, Youssef NF. Derivative spectrophotometric method for simultaneous determination of Ezetimibe and Simvastatin in combined tablets. European J Chem 2010 Dec 1(4): 348-351.
24. Joshi HV, Patel JK, and Kothapalli L. Simultaneous derivative and multicomponent spectrophotometric determination of Simvastatin and Ezetimibe in tabletsDer Pharma Chemica 2010 Feb 2(2): 152-156.
25. Kothari A, Sharma S.Development and validation of spectrophotometric method

for Simultaneous estimation of sitagliptin phosphate andSimvastatin in tablet dosage form Inter J Pharma 2012 Sep 2(3): 609-612
26. Phaneemdra D, Venkatesh V, Ramarao N.2012 Simultaneous estimation of Simvastatin and Sitagliptin by using different analytical methods, Inter J Adv Pharma Anal 2012 Jan 2(1):19-23.
27. D.Phaneemdra G, Nagamalleswari V, Venkatesh AE, Prabahar PV, Suresh NR,Chromatographic and Spectrophotometric Methods for Simultaneous Determination of Simvastatin and Sitagliptin in Combined Dosage Form. Asian Pacific J Trop Biomed 2012: 1-6.
28. Bonde P, Sharma S, Kourav N, Attar AM. Development and validated UV spectrophotometric and RP-HPLC methods for the estimation of Simvastatin and Ezetimibe in combined pharmaceutical dosage form Inter J Curr Trends Sci Tech 2010 Oct 1(3): 135.
29. Sharma S. Development of UV Spectrophotometry and RP HPLC Method and Its Validation for Simultaneous Estimation of Sitagliptin Phosphate and Simvastatin in Marketed Formulation Inter J Pharma Bio Arch 2012 Oct 3(3): 678.
30. Abhishek GJ. Development and Validation of Stability Indicating RP-UPLC Method for Simultaneous Determination in Fixed Dose Combination of Ezetimibe and Simvastatin. Chroma Sep Tech 2012.
31. Kavitha KY, Geetha G, Hariprasad R, Venkatnarayana R, Subramanian G Development and validation of stbility indicating RP- HPLC method for the simultaneous estimation of Sitagliptin phosphate and Simvastatin Inter ResJ Pharma 2012 Dec 3(12):123-127.
32. Raghava KAS, Rao SV, Krishna JA, Satyanand YSVR. Simultaneous estimation of Sitagliptin and Simvastatin in Tablet Dosage Form by A Validated Rp-Hplc Method.Inter J Pharm Sci Rev Res 2012 Mar 15(1): 41-44.
33. Lakka NS, Goswami N, Balakrishna P, Sailaja V. Development and validation of a stability-indicating RP-HPLC for the simultaneous determination of Atorvastatin Calcium and Simvastatin in pharmaceutical solid dosage forms. Int J Res Pharm Sci 2011 Jan2: 608-615.
34. Chaudhari BG, Patel NM, Shah PB. . Determination of Simvastatin, Pravastatin sodium and Rosuvastatin calcium in tablet dosage forms by HPTLC, Indian J Pharma Sci. 2007 Feb 69(1):130.
35. Jain N, Jain R, Swami H. & Jain DK. RP-HPLC Method for Simultaneous Estimation of Simvastatin and Ezetimibe in Bulk Drug and its Combined Dosage FormAsian J Res Chem. 2008 Jan 1(1): 29-31.
36. Shivshanker K, Sreekanth N, Harikrishnan N, Roosewelt C, Rao GS. Gunasekaran V. Validated simultaneous estimation of Simvastatin and Ezetimibe by RP-HPLC in pure and pharmaceutical dosage form Asian J of Chem 2007 Jul 19(6) 4303-4308.
37. Samaa JR, Kalakuntlab RR, Rao VSN, Reddannaa P. Simultaneous estimation of Simvastatin and Ezetimibe in pharmaceutical formulations by RP-HPLC method.J Pharma Sci Res 2010 May 2(2): 82-89.
38. Hefnawy M, Al-Omar M, Julkhuf S. Rapid and sensitive simultaneous determination of Ezetimibe and Simvastatin from their combination drug products by monolithic silica high-performance liquid chromatographic columnJ Pharma Biomed Anal 2009 Sep 50(3): 527-534.
39. Madan J, Thakkar V, Dwivedi AK. Singh S. Ion-pairing RP-HPLC analytical methods for simultaneous estimation of Simvastatin and its hydroxyl acid J Sci Indust Res 2007 Apr 66: 371-376.
40. Nagaraju P.A Validated Reverse Phase HPLC Method for the Simultaneous estimation of Simvastatin and Ezetimibe in Pharmaceutical dosage forms J of Global Pharma Tech. 2010 Dec 2(4):
41. Kumar DA, Sujan DP, Vijayasree V. Rao JVLN. Simultaneous determination of Simvastatin and Ezetimibe in tablets by HPLC.J of Chem. 2009 May 6(2): 541-544.
42. Sultana NS, Arayne M, Naz SS, Shafi N, Naveed SJ. Simultaneous determination of prazosin, atorvastatin, Rosuvastatin and simvastatin in API, dosage formulations and human serum by RP-HPLC, Chinese Chem Soc. 2010 Sep 57(6): 1286.
43. Rahman MU, Parveen G, Nyola NK, Khan S, Talegaonkar S, Yar MS, Khar RK Simultaneous estimation of simvastatin and Ezetimibe in pharmaceutical tablet dosage forms by RP-HPLC: A review Inter J Pharma Res Dev 2(9): 56-62.
44. Neelima B, Kumar PR and Krishna MM, Bindu VH. Prasad YR. Simultaneous estimation of Simvastatin and Ezetimibe by RP-HPLC in pure and pharmaceutical dosage form, Orient J Chem. 2008;24(1): 195-200.
45. Dixit RP, Barhate CR, Nagarsenker MS. Stability-indicating HPTLC method for simultaneous determination of Ezetimibe and Simvastatin, Chromatographia.2008 Sep67(2): 101-107.
46. Chaudhari BG, Patel NM, Shah PB. . Determination of Simvastatin, Pravastatin

sodium and Rosuvastatin calcium in tablet dosage forms by HPTLC2007Mar69(1):130.
47. Dhaneshwar SS, Deshpande P, Patil M, Vadnerkar G, Dhaneshwar. Development and validation of a method for simultaneous densitometric analysis of Simvastatin and Ezetimibe as the bulk drugs and in the tablet dosage formActa Chromatographia 2008 Feb 20(1): 71-79.
48. Rathinaraj S. Development and Validation of A HPTLC Method for the Estimation of Simvastatin and Ezetimibe. Inter J of Pharma Bio Arch 2010; 1(4):222-7.
49. Rathod S, Patil P, Chopade V. Development and Validation of HPTLC method for the estimation of Sitagliptin Phosphate and Simvastatin in bulk and Marketed Formulation Inter J Drug Dev Res Sep 2012 4(3): 292-297.
50. Barrett B, Huclova J, Borek-Dohalsky V, Nemec B & Jelinek I. Validated HPLC–MS/MS method for simultaneous determination of Simvastatin and Simvastatin hydroxy acid in human plasma. J of Pharma Biomed Anal.2012 May 41(2): 517-526.
51. ICH, Validation of Analytical Procedures: Methodology Q_2 (R_1), International Conference on Harmonization, IFPMA, Geneva; 1996.

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