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Quantification of Drugs and Pharmaceuticals Using Chloramine-T and Rhodamine-B Dye: A Spectrophotometric Study

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Abstract: *Simple, sensitive and selective methods are developed for the spectrophotometric determination of drugs, viz., Rosuvastatin Calcium, Alfuzosine hydrochloride, Atorvastatin Calcium, Ibandronate sodium, Imatinib Mesylate based on their reactivity towards Chloramine-T. The method of each drug depends upon oxidation of drugs by Chloramine-T (Excess) and estimating the amount of unreacted Chloramine-T by Rhodamine-B dye at λmax 557nm. These methods have been applied for the determination of drugs in their pure form as well as in tablet formulations. The effect of excipients has also been studied and found to have no effect. These methods have been validated in terms of guidelines of ICH.*

Keywords: *Spectrophotometry, Drugs, Chloramine-T, Rhodamine-B, Quantification, Validation.*

I. Introduction

1.1. Rosuvastatin Calcium:

Rosuvastatin (ROS) is chemically *bis ((E)-7[4-(4-Fluorophenyl)-6*-Isopropyl-2-(Methyl (methyl sulfonyl) aminopyrmidin-5yl) (3R, 5S)-3, 5-dihydroxyhept-6-enoic acid) Calcium salt (Fig.1) it belongs to the class of drugs called statins, which are employed to lower hypercholesterolemia and related conditions and to prevent cardiovascular diseases [1].It is widely used for the treatment of hyperlipidemia. It inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reducatase, the rate limiting enzyme that converts HMG CoA to mevalonate a precursor of cholesterol and thereby checks the synthesis of cholesterol [2]. A survey of literature showed few LC–MS/MS with electro spray ionization method [3-5], UV spectrophotometric [6-8], few HPLC[9-11], RP- HPLC [12,13], HPTLC [14] and Voltametry [15] methods are available for the estimation of Rosuvastatin in pharmaceutical preparation and in biological fluids.

1.2. Alfuzosine hydrochloride:

Alfuzosine (ALF) is chemically known as N-[3-[(4-amino-6, 7-dimethoxy-quinazolin-2-yl)-methyl-amino] propyl] tetrahydrofuran- 2-carboxamide [Fig.2], is an alpha1-Adrenoreceptor blocker. It works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate [16] and a reduction in symptoms of BPH. Several methods have been reported for quantitative determination of ALF in HPLC [17-18], Conductometry [19], Voltametry [20], Colorimetry [21], spectrophotometry [22, 23] and Spectrofluorimetry [24] for bulk drug and Tablets.

1.3. Atorvastatin Calcium:

Atorvastatin calcium(ATV) is chemically named as(3R,5R)-7-(2-[4-Fluorophenyl] - 3-phenyl-4-[phenylcarbamoyl]-5-propan-2-ylpyrrol-1-yl)-3, 5-dihydroxyheptanoic acid (Fig. 3).It is a member of the drug class known as statins, which are used primarily for lowering blood cholesterol and for prevention of events associated with cardiovascular disease. Atorvastatin is a Competitive inhibitor of HMG-CoA reductase. This enzyme catalyzes the reduction of -hydroxy-3-methylgultaryl-coenzyme-A to mevalonate, which is the rate-determining step in hepatic Cholesterol synthesis. Because cholesterol synthesis decreases, Hepatic cells increase the number of LDL receptors on the surface of. The cells, which in turn increase the amount of LDL uptake by the Hepatic cells, and decrease the amount of LDL in the blood [25, 26]. Several methods have been reported for quantitative determination of ATV in HPTLC[27, 28], RP-HPLC [29], HPLC [30], Spectrophotometric method [31] and aqueous samples method [32] for bulk drug and Tablets.

1.4. Ibandronate sodium:

Ibandronate sodium (IBD) is one of the nitrogene carrying Bisphosphonate. According to IUPAC nomenclature it is 3-(N-methyl-N-pentyl) amino-1-hydroxypropane-1, 1-diphosphonic acid, sodium salt, monohydrate (Fig.4). It prevent osteoclast-conciliate boneresorption [33]. It is precious for the cure of hypercalcemia of malignancy [34], Paget's disease, postmenopausal osteoporosi and corticosteroid-induced

osteoporosis metastatic bone disease [35]. Several methods have been reported for quantitative determination of IBD in UV [36], Ion chromatography and ion pair chromatography [37-39], electrophoresis method [40] for bulk drug and Tablets.

1.5. Imatinib Mesylate:

Imatinib mesylate (ITM) is a most frequently prescribed cancer medication drug to treat leukemia and gastrointestinal tumors. The drug is designed to inhibit tyrosine kinases such as Bcr-Abl and is used in the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor [41]. Imatinib mesylate was approved by the US Food and Drug Administration (FDA) to treat a rare cancer called chronic myeloid leukemia (CML) [42]. Imatinib mesylate is chemically known as 4-4[(4-methyl-1- piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino] phenyl] – benzamide mono methane sulfonate (Fig.5). Literature survey reveals that several analytical methods like UV spectrophotometric [43], HPLC [44], Charge Transfer complex [45], RP-HPLC [46] methods are reported for estimation of Imatinib mesylate in bulk drug, formulations, pure active pharmaceutical ingredient and tablet dosage form.

Thorough survey of literature on the above mentioned drugs revealed that quantification using Chloramine-T as oxidizing reagent has not been reported yet although the reagent is common, known to offer simple, sensitive method of quantification for drugs This prompted the authors to develop quantification methods for the above cited drugs using Chloramine-T as an oxidizing agent and Rhodamine-B as analytical reagent

II. Structures Of The Drugs

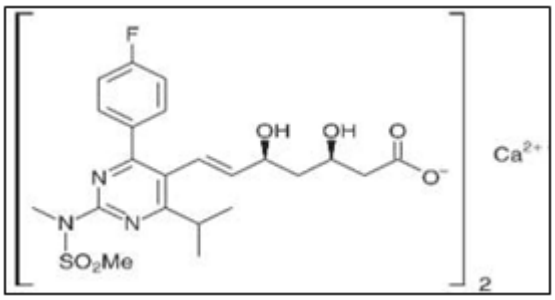

Fig.1 Rosuvastatin Calcium

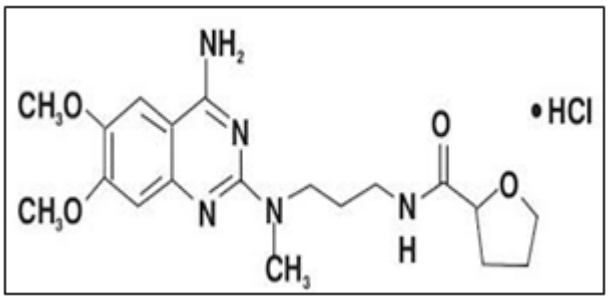

Fig.2 Alfuzosine hydrochloride

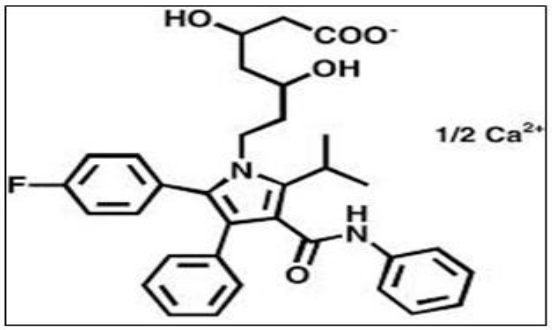

Fig.3 Atorvastatin calciu

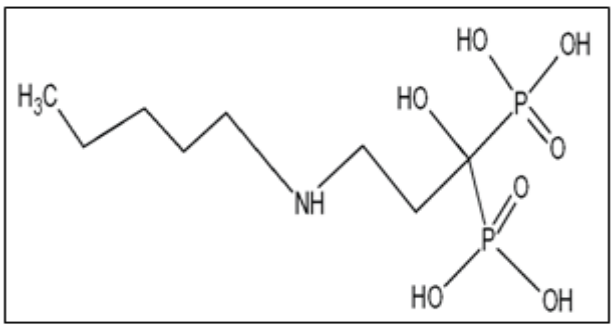

Fig. 4 Ibandronate sodium

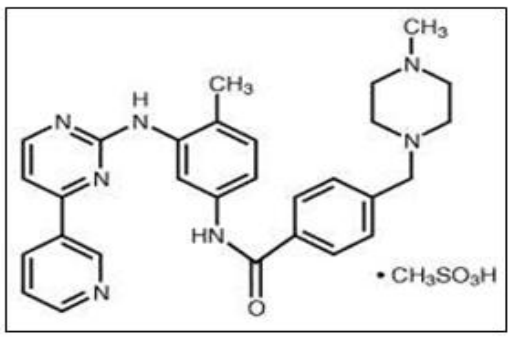

Fig.5 Imatinib Mesylate

III. Materials And Methods

1.6. Instrument

All absorbance measurements were recorded on Shimadzu 140 double beam spectrophotometer as well as Elico 210 UV- Visible double beam & Elico 159 UV- Visible single beam spectrophotometers using matched pair of Quartz cells of 10mm path length.

Chloramine-T solution (0.005mol L–1) was prepared by dissolving 0.1408g Chloramine-T (Finar chemicals limited, Ahmadabad, India) in 100mL standard flask with distilled water. This solution was diluted with water appropriately to get 45µg mL–1 Chloramine-T for use in spectrophotometric method.

A stock solution of Rhodamine B (500µg mL–1) was prepared by dissolving the dye (S. D. Fine Chem. Ltd., Mumbai) in water and filtered using glass wool. The dye solution was diluted to get working concentration of 50µg mL^{-1}.

Hydrochloric acid (S.D. Fine Chem., Mumbai, India; sp. gr. 1.18) was diluted appropriately with water to get 2M acid.

The pharmaceutical grade drugs were supplied by Arabindo pharmaceuticals and hetero drugs Pvt. Lmt. Hyderabad. A stock standard solution of drugs was prepared by dissolving accurately weighed 20mg of pure drug in water and diluting to 100mL in a calibrated flask with water. The solution was diluted stepwise to get working concentrations.

1.7. Assay procedure

Aliquots of pure drug solution (1 to 7mL) were transferred into a series of 10mL calibrated flask. To each flask, 1 mL of 2 mol L–1 hydrochloric acid was added, followed by 1 mL of Chloramine-T solution (45 µg mL1). The contents were mixed and the flasks were set aside for 15min under occasional shaking. Finally, 1mL of 50 µg mL–1 Rhodamine- B solution was added to each flask, diluted to the mark with water and the absorbance of solution was measured at 557 nm. Calibration curves were constructed for all the drugs by plotting the absorbance versus the concentration of drugs. The absorbance data was collected for six replicate experiments and absorbance to concentration ratio called the relative response was determined. The relative responses from 95% to 105% of average only are considered for

1.8. Construction of the Calibration curves (Fig.6).

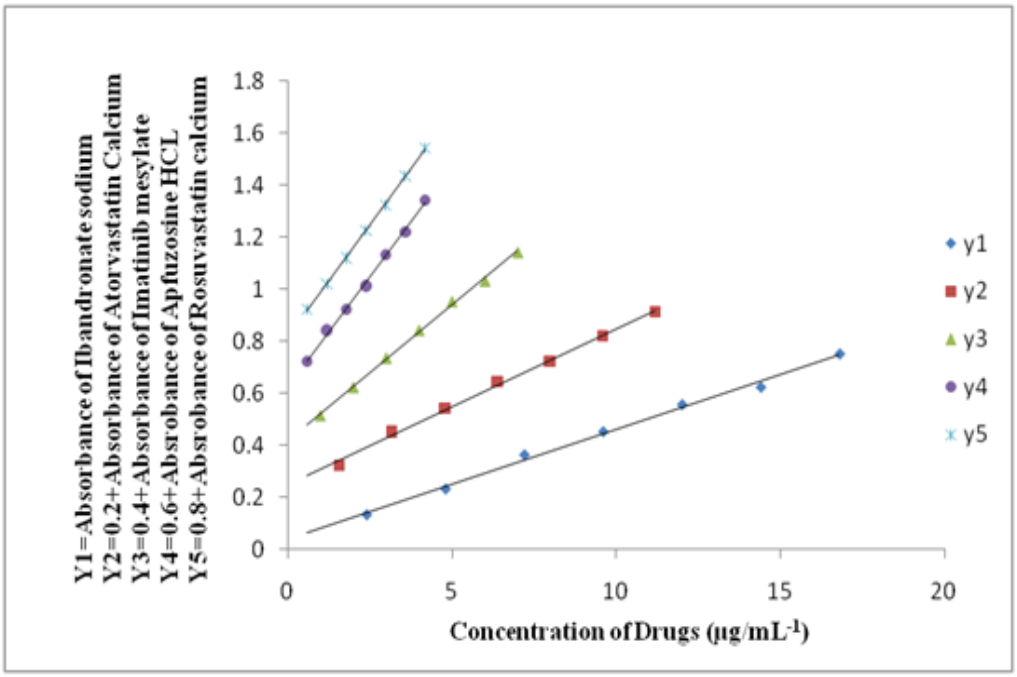

Fig.6 Calibration curves of ROSU, ALF, ATV, IBD, and ITM.

IV. Procedure For Assay Of Pure Drug

Sample solutions of each drug in the beer's law limits were chosen and recovery experiments were performed to check the accuracy and precision. The concentration chosen and recovery are tabulated in table 2. For this purpose standard deviation method has been adapted. Excellent recovery and %RSD being less than 2 speaks about the precision and accuracy of the methods.

V. Procedure For Tablets

1.9. Rosuvastatin Calcium

Four tablets (ROSU, 250mg) were weighed and grounded. The powder equivalent to 20mg Rosuvastatin Calcium was stirred well with methanol, sonicated about 30 minutes. The solution was filtered through Whatmann filter paper in a 100mL volumetric standard flask and the residue was washed well with methanol for complete recovery of the drug and methanol was evaporated. The residue was dissolved in 100mL of distilled water and it was further diluted to get required concentration for the analysis of the drug.

1.10. Alfuzosine

Ten tablets of Alfoo were weighed accurately and powdered. The powder equivalent to 50 mg was transferred into a 100 ml volumetric flask, containing a mixture of distilled water (`10.0 ml) and HCL (2.0 ml). The flask was shaken for 5 minutes and the solution was filtered using Whatmann filter paper no.41 and further diluted with water to obtain working standard solution.

1.11. Atorvastatin Calcium

Three tablets (Atorvastatin calcium 10mg) were weighed accurately and crushed to a fine powder and the powder equivalent to 10mg of Atorvastatin calcium was weighed accurately and transferred to 100 ml volumetric flask, dissolved in sufficient quantity of methanol, sonicated for 10 min and the volume was finally diluted to the mark with methanol. This solution was mixed well and filtered through Whatmann filter paper No. 42. It was used as stock sample solution and was further diluted with the same solvent to get working standard solution.

1.12. Ibandronate sodium (IBD)

Four tablets (IBD, 250mg) were weighed and grounded. The powder equivalent to 20mg Ibandronate sodium (IBD) was stirred well with methanol, sonicated about 30 minutes. The solution was filtered through Whatmann filter paper in a 100mL volumetric standard flask and the residue was washed well with methanol for complete recovery of the drug and methanol was evaporated. The residue was dissolved in 100mL of distilled water and it was further diluted to get required concentration for the analysis of the drug.

1.13. Imatinib Mesylate

For the analysis of pharmaceutical formulations two tablets (veenat – 100mg) were weighed accurately and grounded. A quantity equivalent to 10mg of Imatinib mesylate was weighed accurately, transferred into a 100 mL calibrated flask and the volume was finally diluted to the mark with double distilled water, mixed well and filtered using a Whatmann filter paper No. 42 filter paper. It was used as stock sample solution and was further diluted with water to get working standard solution

VI. Results And Discussion

1.14. Analytical data

A linear correlation was found between absorbance at λ max and concentration of all drugs in the ranges given in Table 1. Regression analysis of the Beer's law data using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) for each system and the values are presented in Table 1. The optical characteristics such as Beer's law limits and Sandell sensitivity values for both methods are also given in Table 1. The limits of detection (LOD) and quantification (LOQ) calculated according to ICH guidelines are also presented in Table 1 and reveal the very high sensitivity of the methods

1.15. Precision and Accuracy

Intra-day precision was assessed from the results of six replicate analyses on pure drug solution. The mean values and relative standard deviation (RSD) values for replicate analyses at three different levels (amounts/concentrations) were calculated. To evaluate the inter-day precision, analysis was performed over a period of five days, preparing all solutions afresh each day. The accuracy of the methods was determined by calculating the percentage deviation observed in the analysis of pure drug solution and expressed as the relative error. Table 2 summarizes the intra-day precision and accuracy data for the assay of pure drugs solution by the proposed methods.

Table 1: Analytical and Regression Parameters of Spectrophotometric Method

Parameter	ROSU	ALF	ATV	IBD	ITM
λmax, nm	557	557	557	557	557
Beer's law limits μg mL^{-1}	0.6-4.2	0.6-4.2	1.6-11.2	2.4-16.8	1-7
Molar absorptivity, L mol^{-1} cm^{-1}	$2.052x10^5$	$8.596x10^4$	$8.838x10^4$	$1.977x10^4$	$6.614x10^4$
Sandell sensitivity* μg cm^{-2}	0.006	0.006	0.017	0.024	0.010
Limit of detection μg mL^{-1}	0.185	0.280	0.442	0.475	0.243
Limit of quantification μg mL^{-1}	0.560	0.848	1.340	1.441	0.735
Regression equation, Y**					
Intercept, (a)	0.014	0.024	0.046	0.039	0.015
Slope, (b)	0.172	0.169	0.060	0.042	0.104
Correlation coefficient, (r)	0.999	0.998	0.996	0.995	0.998
Standard deviation of intercept (Sa)	0.010	0.014	0.008	0.006	0.008
Standard deviation of slope (Sb)	0.002	0.005	0.002	0.001	0.004

*Limit of determination as the weight in μg per mL of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm2 and path length of 1 cm. Y**= a+bX, where Y is the absorbance and X concentration of drugs in μg per mL

Table 2: Determination of Accuracy and Precision on Pure Drug Samples Application to formulations

Drug	Taken (μg/ml)	Found (μg/ml)	Error (μg/ml)	Recovery (%)	RSD(%)	Proposed method Mean ± SD
ROSU	1.5	1.52	1.33	101.33	0.966	100.33± 1.000
	3.0	2.98	0.67	99.33		
	6.0	6.02	0.33	100.33		
ALF	3.0	2.99	0.33	99.66	0.353	100.04 ± 0.354
	5.5	5.52	0.36	100.36		
	9.0	9.01	0.11	100.11		
ATV	3.0	2.96	1.33	98.66	0.885	99.68 ±0.883
	6.0	6.01	0.16	100.16		
	9.0	9.02	0.22	100.22		
IBD	40	40.02	0.05	100.05	0.0556	100 ± 0.0556
	50	49.97	0.06	99.94		
	60	60.01	0.01	100.01		
ITM	3.0	2.98	0.67	99.33	0.424	99.72±0.423
	6.0	6.01	0.17	100.17		
	9.0	8.97	0.33	99.66		

The proposed methods are applied to the determination of drugs in tablets. The results in Table 3 showed that the methods are successful for the determination of drugs and that the excipients in the dosage forms do not interfere. The results are compared to the available validated reported methods on each drug and the results agree well with the claim and also are in agreement with the results obtained by the literature method. Statistical analysis of the results using Student's t-test for accuracy and F-test for precision revealed no significant difference between the proposed methods and the literature method with respect to accuracy and precision.

Table 3: Results of assay of tablets by the proposed methods and statistical evaluation method

Tablets	Drug in tablet (µg mL^{-1})	Drug added (µg mL^{-1})	Total found mL^{-1}	Error (%)	Recovery (%)	RSD (%)	Reference method[6-10] Mean ± SD	Proposed Method	t-test	F-test
ROSU	0.50 0.50 0.50 2.0 3.0 4.5	1.0 2.0 3.0 0.0 0.0 0.0	1.504 2.48 3.53 2.02 2.98 4.45	0.27 0.8 0.86 1 0.67 1.11	100.27 99.2 100.86 101 99.33 98.88	0.9077	100±1.070	99.92±0.907	0.2849 (2.447)	0.71853 (3.05455)
ALF	3.0 6.0 9.0 12 5.0 4.0	1.0 1.0 1.0 1.0 0.5 1.0	3.97 6.98 9.99 13.0 5.52 4.98	0.75 0.29 0.1 0.0 0.363 0.4	99.25 99.71 99.9 100 100.36 99.6	0.3786	100.6±0.6	99.80±0.3779	0.7176 (1.943)	0.397 (3.10751)
ATV	0.50 0.50 0.50 3.0 6.0 9.0	1.0 2.0 3.0 0.0 0.0 0.0	1.50 2.48 3.51 2.97 6.01 9.03	0.00 0.8 0.29 1 0.16 0.33	100.00 99.2 100.28 99 100.16 100.33	0.5800	100.03±0.409	99.82±0.57897 9	0.586 (2.447)	2.004 (3.05455)
IBD	40 50 60 40 50 60	0.0 0.0 0.0 5.5 5.5 5.5	40.00 49.98 60.00 45.52 55.51 65.53	0 0.04 0 0.043 0.01 0.046	100 99.96 100 100.04 100.01 100.04	0.0299	100.63±1.52	100.008±0.029 94	2.4009 (2.447)	3.878 (3.05455)
ITM	0.50 0.50 0.50 3.0 6.0 9.0	3.0 6.0 9.0 0.0 0.0 0.0	3.51 6.47 9.52 3.00 5.98 9.01	0.28 0.46 0.21 0 0.33 0.11	100.28 99.53 100.21 100.00 99.66 100.11	0.3046	100.5±0.55	99.965±0.3045	0.9567 (2.447)	0.3065 (3.05455)

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References

[1]. Kaila HO, Ambasana MA, Thakkar RS, Saravaia HT, Shan AK. A New improved RP-HPLC Method for assay of rosuvastatin calcium in tablets. Indian J of Pharmaceutical Sciences 2010; 72: 592-598.

[2]. S.C. Sweetman Martindale-The Complete Drug Reference (thirty-sixth ed.), 1The Pharmaceutical Press, London, UK (2009) pp. 1218–1219, 1238–1239, 1284–12851310, 1307–1310.

[3]. Trivedi R.K. Kallem R.R. Mullangi R. Srinivas N.R., Simultaneous determination of rosuvastatin and fenofibric acid in human plasma by LC–MS/MS with electrospray ionization: Assay development, validation and application to a clinical study, J Pharma Biomed Anal., 2005, 39, 661-669.

[4]. Xu D.H. Ruan Z.R. Zhou Q. Yuan H. Jiang B., Quantitative determination of rosuvastatin in human plasma by liquid chromatography with electrospray ionization tandem mass spectrometry, Rapid Commun Mass Spectrum., 2006, 20, 2369-2375.

[5]. Kallem R.R. Karthik A. Chakradhar L. Mullangi R. Srinivas N.R., Development and validation of a highly sensitive and robust LC-MS/MS with electrospray ionization method for quantification of rosuvastatin in small volume human plasma samples and its application to a clinical study, Arzneimittel forsch., 2007, 57, 705-11.

[6]. Uyar B. Celebier M. Altinoz S., Spectrophotometric determination of rosuvastatin calcium in tablets, Pharmazie. 2007, 62, 411-413.

[7]. Rekha, Rajeevkuma, *, S. Anbazhagan1, P. Rajeev Kumar2and K. Nimesh , Novel Simultaneous Determination of Rosuvastatin Calcium and Fenofibrate in Tablet Formulation by Derivative Spectrophotometry, International Journal of Research in Pharmaceutical and Biomedical Sciences, ISSN:2229-3701,2011.

[8]. G. Sree, Chandini Saha, elatha, Md. Nazeeruddin, Spectrophotometric Estimation of Rosuvastatin Calcium in Bulk & Pharmaceutical Formulations, Int.J. Pharmacy and Analytical Research vol-2(3) 2013

[9]. Singh S.S. Sharma K. Patel H. Jain M. Shah H. Gupta S. Thakkar P. Patel N. Singh S.P. Lohray B.B., Estimation of Rosuvastatin in human plasma by HPLC tandem mass spectroscopic method and its application to bioequivalence study, J. Braz. Chem. Soc., 2005, 16, 944-950.

[10]. Vittal S. Shitut N.R. Kumar T.R. Vinu M.C. Mullangi R. Srinivas N.R., Simultaneous quantitation of rosuvastatin and gemfibrozil in human plasma by high-performance liquid chromatography and its application to a pharmacokinetic study, Biomed chromatography., 2006, 20, 1252-1259.

[11]. Validated High-Performance Liquid Chromatographic Method for the Estimation of Rosuvastatin Calcium in Bulk and Pharmaceutical Formulations, Int J Biomed Sci. 2011 Dec; 7(4): 283–288.

[12]. D Dipali Tajane*, Amol M.Raurale, Pradeep D. Bharande, Anil N.Mali, Amol V.Gadkari, Vishal R.Bhosale, development and validation of a RP-HPLC-PDA method for simultaneous determination of Rosuvastatin calcium and Amlodipine besylate in pharmaceutical dosage form Journal of Chemical and Pharmaceutical Research, 20 12, 4(5):2789-2794.12, 4(5):2789-2794 .

[13]. Muthy TGK and Geethanjali J, Validated RP-HPLC Method for Simultaneous Estimation of Metformin Hydrochloride and Rosuvastatin Calcium in Bulk and In-House Formulation Journal of Chromatography & Separation Techniques ISSN: 2157-7064 J Chromatogram Sep Tech 5:252. December 05, 2014.

[14]. Rani S. Potawale, Satish Y. Gabhe , HPTLC Method For Simultaneous Determination Of Rosuvastatin And Fenofibrate In Bulk And Pharmaceutical Formulation, , International Journal Of Pharmacy And Pharmaceutical Sciences, Vol 6issue 7, 2014.

[15]. Sacide Altınöz*a and Banu Uyara Electrochemical behavior and voltammetric determination of rosuvastatin calcium in pharmaceutical preparations using a square-wave voltammetric method Analytical Methods, issue 20, 2013,**5**, 5709-5716.

[16]. Radha, G. V. Santosh Naidu, M. 1.Design of transdermal films of alfuzosin HCl by using a natural polymer tamarind seed polysaccharide extract, Scholars Research Library Der Pharmacia Letter, 2013; 5 (3):457-464.

[17]. Dhoka, Madhura V.; Harale, Rupali B.; Bhankele, Sonal C.; Damle, Mrinalini C.; Vidwans, Omkar S.; Kshirsagar,Sanjay J., Development, validation and comparative statistical evaluation of HPLC and HPTLC method for determination of Alfuzosin in human plasma., Journal of Chemical and Pharmaceutical Research (2012), 4(6), 3207- 3214

[18] .Shakya, Ashok K.; Arafar, Tawfiq A.; Abuawaad, Ahmad; Al-Hroub, Hamza; Melhim, Munther., Simple and rapid HPLC method for the determination of alfuzosin in human plasma., Jordan Journal of Pharmaceutical Sciences (2010), 3(1), 25-36

[19] .Safwan Ashour*and Mouhammed Khateeb, Conductometric Titration Method for Determination of Alfuzosin Hydrochloride and Fexofenadine Hydrochloride Using Sodium Tetraphenylborate. Canadian Chemical Transactions, 2013; 1 (4): 292-304.

[20]. Rashedi, H.; Norouzi, P.; Ganjali, M. R., Determination of alfuzosin by hybrid of ionic liquid-graphenenano-composite film using coulometric FFT linear sweep voltammetry.,International Journal of Electrochemical Science (2013), 8(2), 2479-2490

[21]. Ishaq, B. Mohammed; Prakash, K. Vanitha; Kumar, C. Hari; Rani, G. Usha; Ramakrishna, P., Colorimetric determination of alfuzosinHCl in pharmaceutical formulations., Journal of Pharmacy Research (2011), 4(1), 226-228

[22]. Al-Tamimi, Salma A.; Aly, Fatma A.; Almutairi, Adibah M., Kinetic spectrophotometric methods for the determination of alfuzosin hydrochloride in bulk and pharmaceutical formulations., Journal of Analytical Chemistry (2013), 68(4), 313-320

[23]. El-Arfaj, N.; Abdel-Razeq, S.; El-Dosarry, S., Spectrophotometric methods for the determination of alfuzosin-HCl and carvedilol in their formulations. Egyptian Journal of Analytical Chemistry (2009), 18, 80-91

[24]. Razeq, Sawsan A., Spectrofluorimetric method for the determination of alfuzosin and flavoxate hydrochlorides in pharmaceuticals and biological fluids. Egyptian Journal of Analytical Chemistry (2008), 17, 127-138

[25]. Lipitor product information. Park-Davis/Pfizer Inc. April 2002

[26]. Burnham TH. HMG-CoA reductase inhibitors. In: ed. Drug Facts and Comparisons. Louis: Facts and Comparisons, 2002; Inc 536-542a

[27]. SB Wankhede, NR Dixi, Stability indicating HPTLC method for quantitative determination of atorvastatin calcium and metoprolol succinate in capsules, - Der Pharmacia Sinica Journal, 5(1), 89-93. 3. 2011.

[28]. Ginoya Charmi G, Dinesh V. Thakkar, Ginoya Charmi G Et Al, Development And Validation Of HPTLC Method For Simultaneous Determination Of Metoprolol Succinate And Atorvastatin Calcium In A Pharmaceutical Dosage Form International Research Journal Of Pharmacy, . Irjp 2013, 4(2) Page 102

[29]. Suresh Kumar GV1*, Rajendraprasad Y, Chandrashekar SM, Development and validation of reversed-phase HPLC method for Simultaneous Estimation of Atorvastatin calcium and Telmisartan in Tablet dosage form, International Journal of PharmTech Research, ISSN : 0974-4304, Vol.2, No.1, pp 463-470, Jan-Mar 2010.

[30]. Stability-indicating HPLC method for the simultaneous determination of pantoprazole, rabeprazole, lansoprazole and domperidone from their combination dosage form, Vaithiyanathan Sree Janardhanan*, Rajappan Manavalan and Kannappan Valliapp, International Journal of Drug Development & Research October-December 2011, Vol. 3, Issue 4, ISSN 0975-9344.

[31]. Capsules Sagar B. Wankhede*, Nitin R. Dixit, Sohan S. Chitlange, Validated spectrophotometric methods for quantitative determination of Atorvastatin calcium and Metoprolol succinate in, Der Pharma Chemical , 2010, 2(1): 134-140 ISSN 0975-413X , 134

[32]. Xiu-Sheng, M. and C.D. Metcalfe, Determination of cholesterol-lowering statin drugs in aqueous samples using liquid chromatography-electrospray ionization tandem mass spectrometry. J. Chrom B., 998: 133-14, 2003.

[33]. Muller R, Hannan M, Smith SY, Bauss F.Intermittent ibandronate preserves bone quality and bone strength in the lumbar spine after 16 months of treatment in the ovariectomized cynomolgus monkey. J of Bone Min Rese 2004; 19:1787-1796

[34]. Pecherstorfer M, Herrmann Z, Body JJ, Manegold C. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J of Clinical Oncology 1996; 14:268-276

[35]. Coleman RE, Purohit OP, Black C, Vinholes JJ. Double-blind, randomized, placebo-controlled study of oral ibandronate in patients with metastatic bone disease Annals of Oncol 1999; 10: 311-316

[36]. Anonymous, ICH, Q2 (R1). Validation of analytical procedures: Text and Methodology International conference on Harmonization, Geneva. 2005; 1-13

[37]. Jiang, Y., Xie, Z., Determination of Ibandronate and its degradation products by ion-pair RP LC with evaporative light-scattering detection, Chromatographia, 62, **2005,** 257-261.

[38]. Han, Y. H. R., Qin, X. Z., Determination of Alendronate sodium by ion chromatography with refractive index detection, J. Chromatogram. A, 719, **1996,** 345-352.

[39]. Tsai, E. W., Ip, D. P., Brooks, M. A., Determination of Alendronate in pharmaceutical dosage formulations by ion chromatography with conductivity detection, J. Chromatogram., 596, **1992,** 217-224.

[40]. Bertinatto R. J., A. Desimone, M. F., Iglesias, S. L., Giorgieri, S. A., Diaz, L. E., Validation of a capillary electrophoresis method for the analysis of ibandronate related impurities, J. Pharm. Biomed. Anal., 44, **2007,** 305-308.

[41]. Drug Repurposing Identifies a Synergistic Combination Therapy with Imatinib Mesylate for Gastrointestinal Stromal Tumor Ziyan Y. Pessetto, Yan Ma, Jeff J. Hirst, Margaret von Mehren2,Scott J. Weir, and Andrew K. Godwin, Mol Cancer Ther, October 2014; 13: 2276.

[42]. Imatinib-Wikipedia, (http://en.wikipedia.org/wiki/Imatinib). Accessed, 03 March 2015

[43]. Patil SJ, Doijad RC and Dhumal PP: Development of UV-Spectrophotometric Method for determination of Imatinib Mesylate in Bulk & Formulation. Asian Journal of Pharmaceutical and Clinical Research, 2013; 6: 54-57.

[44]. Quantitative determination of imatinib stability under various stress conditions Khalid Mohammed Alkharfy, Rao Muzaffer Ali Khan, Majed Al-Asmari, Baderelddin Hashim Alhadeyah, Ajaz Ahmad, Journal of pharmacy & BioAllied sciences, 2013; 5(1): 49-52.

[45]. Spectrophotometric Determination of Imatinib Mesylate using Charge Transfer Complexes in Pure Form and Pharmaceutical Formulation, Shereen. E. Abdel KarimRasha. M. El- NasharAshraf. H. Abadi, 12/2014; 2(3): 55-63.

[46]. A Rapid Reverse Phase HPLC Dissolution Method Development And Validation Of Imatinib In Imatinib Mesylate Tablets Dosage Form Shah P 1,3, Shah N 2 , Brahmbhatt R1 , Saptarshi D 1 , Shah R 3, International Journal Of Pharmaceutical Research And Bio-Science, 2277-8713 Shah P, Ijprbs, 2014; 3(4): 64-82.