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VALIDATION & FORMULATION DEVELOPMENT OF DRUG "EZETIMIBE" SOLUBILITY ENHANCEMENT BY HYDROTROPIC SOLUBILIZATION TECHNIQUE

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ABSTRACT

In the proposed method Ezetimibe estimated by hydrotropic phenomena. The drug Ezetimibe was physically characterized on the beginning of appearance, color and odor. The Melting point of Ezetimibe was found 163-164°C. Enhancement of solubility was more than 60 to 70% for Ezetimibe respectively in mixed hydrotropic solution, 2M Ammonium Acetate: 2M Sod. Citrate (1:1). The enhancement of solubility of Ezetimibe was observed because of the hydrotropic solubilization phenomenon. Linearity of both drugs was established by response ratios of drugs. Ezetimibe showed linearity in the concentration range of 10-50 µg/ml Calibration curve was plotted, absorbance versus concentration using λ_{max} of 244nm. The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100%, 120%. In conclusion the developed methods were found simple, sensitive and economical for the simultaneous estimation of selected active pharmaceutical ingredients in their tablet formulation. Validation of developed methods was performed according to ICH guidelines. the proposed methods can be successfully applied for determination and dissolution testing of selected drugs in commercial formulation.

KEYWORDS: Hydrotropy, Ezetimibe, Validation, Analysis, Estimation.

INTRODUCTION

The current main problem in the pharmaceutical industry is related to strategies that augment the aqueous solubility of drugs, as almost 70% of the newly discovered drug candidates

suffer from poor aqueous solubility.[1] Solubility is one of the prime features to accomplish desired pharmacological response.[2] Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to solubility of drug moiety.[3]

In 1916, Carl A. Neuberg coined the word 'hydrotropy'. Hydrotropes possess the ability to increase the solubility of sparingly soluble and poorly soluble drugs in water.[4] It is a molecular phenomenon, adding a second solute (i.e. hydrotrope) helps to increase the aqueous solubility of poorly soluble drug.[5] The presence of a excess quantity of one solute enhances the solubility of another solute.[6] Hydrotropic agents as ionic organic salts which has capacity to increase or decrease the solubility of solute in a given solvent through 'salt in' or 'salt out' effects, respectively.[7] Salts which show 'salt in effect' of non electrolytes is called "hydrotropic salts" and the phenomenon is known as "hydrotropism". They do not exhibit any colloidal properties but they improve solubility by forming weak interaction with solute molecules.[8] A hydrotropic molecule interacts with a less water-soluble molecule as weak van der Waals interactions as π–π or dipole– dipole interaction.[9]

The main objective of this study was to development and validation of method for the analysis of ezetimibe by hydrotropy using UV spectrophotometry.

EXPERIMENTAL WORK

Identification and characterization of drug

Physical characterization of drug: The drug Ezetimibe was physically characterized on the beginning of appearance, color and odor. All these parameters were recorded and compared with the literature, found comprised.

Melting point determination: The melting point determined used for the strength of mind of melting point of Ezetimibe by the open capillary methods. The melting point of drug was recorded and compared with literature values. The Melting point of Ezetimibe was found to be 163-164°C.

FT-IR study carried out by KBr press pellet technique: The concentration of the sample in KBr should be in the range of 0.2% to 1%. The pellet is a lot thicker than a liquid film, consequently a decrease concentration in the sample is required (Beer's Law). For the die set that you'll be the usage of, about 80 mg of the mixture is wanted. Too

excessive of an attention causes typically difficulties to obtain clean pellets. This pellet keeps into the sample cell and scanned between 4000-400 cm^{-1} and IR spectra are obtained.

The FT-IR spectra of Ezetimibe can be divided into four main regions: 3000-2600 cm^{-1}, 2400-1800 cm^{-1}, 1700-1200 cm^{-1}, and 1100-400 cm^{-1}. In the 3000-2600 cm^{-1} region, the strong absorption band at 2928.0458 cm^{-1} is due to the C-H stretching vibrations of aliphatic CH_3 and CH_2 groups.

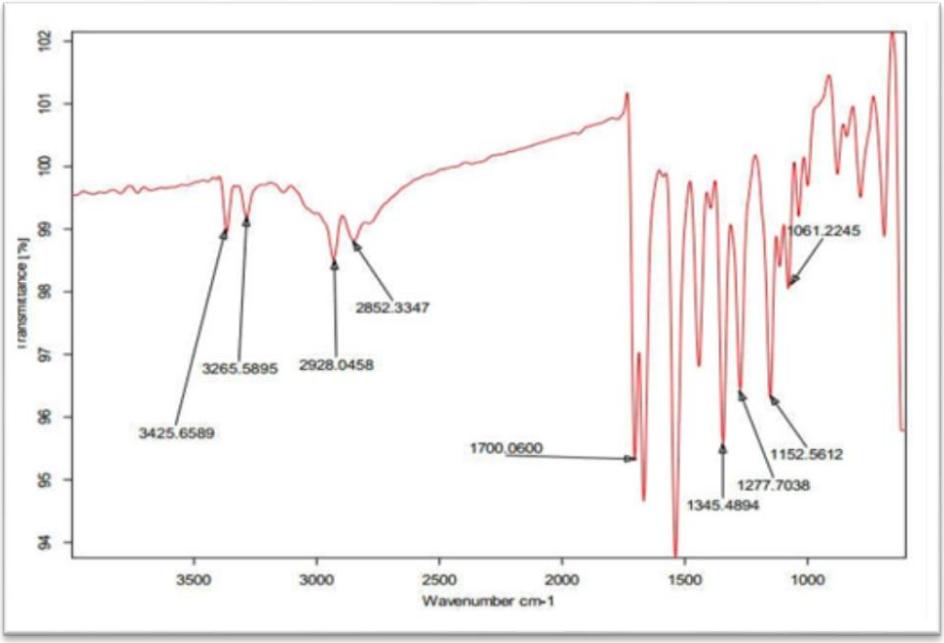

Figure 6.1: FT-IR Spectrogram of Ezetimibe.

The second absorption band at 2852.3347 cm^{-1} is due to the aliphatic C-H in-plane bending vibrations. The third absorption band at 1345.4894 cm^{-1} is due to the symmetric stretching vibrations of C-O bonds. In the 2400-1800 cm-1 region, the strong absorption band at 1700.0600 cm^{-1} is due to the C=O stretching vibrations of the ester group. The second absorption band at 1545.6589 c cm^{-1} is due to the C-C stretching vibrations. The second absorption band at 890.2365 cm^{-1} is due to the O- H bending vibrations of hydroxyl groups.

Method development

In the proposed method Ezetimibe estimated by hydrotropic phenomena Ezetimibe launched in the market for the treatment of It's used to treat high blood cholesterol. Available in the strength of 10mg. till date there is no method for the spectrophotometric

estimation of Ezetimibe by using hydrotropy. "Ezedoc Tablets (10mg)" marketed formulation was estimated by using dye drug reaction.

Solubility: Solubility of Ezetimibe was determined at 25±1°C. Accurately weighed 10 mg Ezetimibe was added in 10 ml volumetric flask containing different solvent and placed at mechanical shaker for 8 hrs. After 8 hrs filter both solution were filtered through whatman filter paper No. 41. The filtrates were diluted suitably and analyzed visually as per I.P.

Table 6.2: Solubility of Drug in Different Solvents.

S. No.	Solvents	Solubility
1	Water	Slightly soluble
2	0.1 N HCl	Soluble
3	0.1 N NaOH	Slightly soluble
4	Methanol	Soluble
6.	Ethanol	Freely soluble

Solubility of Ezetimibe was determined at 25±1°C. Accurately weighed 10 mg Ezetimibe was added in different 10 ml volumetric flask containing different solvent and placed at mechanical shaker for 8 hrs. After 8 hrs filter both solution were filtered through Whattman filter paper No. 41. The filtrates were diluted suitably and analyzed visually table 6.3.

Table 6.3: Solubility of drug in different solvents.

S. No.	Solvents	Solubility of Ezetimibe
1	Water	-+
2	Hot water	-+
3	Cold water	-+
4	2M Sodium acetate	+
5	8M Urea	+
6	2M Sodium Citrate	+
7	2M Sodium Benzoate	+
8	2M Ammonium Acetate	++
9	2M Sod. Citrate	++
10	2M Sodium acetate: 2M Sodium Benzoate(1:1)	+
11	2M Urea:2M Sodium acetate (1:1)	+
12	2M Sodium citrate:8M Urea (1:1)	+
13	2M Sodium citrate:8M Urea (1:1)	+
14	2M Ammonium Acetate: 2M Sod. Citrate(1:1)	+++

(-) Insoluble, (-+) Slightly soluble, (+), Sparingly soluble (++) Soluble, (+++) Freely soluble

Determination of Solubility Enhancement by UV VIS. Spectroscopy: Solubility studies were performed in distilled water 2M Sodium acetate, 8M Urea, 2M Sodium Citrate, 2M Sodium Benzoate, 2M Ammonium Acetate, 2M Sod. Citrate, 2M Sodium acetate: 2M Sodium Benzoate, 2M Urea: 2M Sodium acetate, 2M Sodium citrate: 8M Urea, 2M Sodium citrate: 8M Urea, 2M Ammonium Acetate: 2M Sod. Citrate at room temperature (25 ± 2^0C). An excess amount of drug was added to 100ml of solvent in screw-capped glass vials; these were mechanically shaken for 48 hours at 25°C until equilibrium was achieved. Aliquots were withdrawn, filtered through a membrane filter (0.45µm) and spectrophotometrically analyzed for solubility.

Table 6.4: Results of solubility enhancement by UV VIS. Spectroscopy.

S. No.	Solvents	Solubility Enhancement folds)
1	2M Sodium acetate	5
2	8M Urea	3
3	2M Sodium Citrate	2
4	2M Sodium Benzoate	5
5	2M Ammonium Acetate	8
6	2M Sod. Citrate	9
7	2M Sodium acetate: 2M SodiumBenzoate (1:1)	5
8	2M Urea:2M Sodium acetate (1:1)	4
9	2M Sodium citrate:8M Urea (1:1)	4
10	2M Sodium citrate:8M Urea (1:1)	5
11	2M Ammonium Acetate: 2M Sod.Citrate (1:1)	20

Enhancement of solubility was more than 60 to 70 % for Ezetimibe respectively inmixed hydrotropic solution, 2M Ammonium Acetate: 2M Sod. Citrate (1:1). The enhancement of solubility of Ezetimibe due to the hydrotropic solubilization phenomenon. Results of solubility in different solvent for both the drug were shownin table above.

Selection of solvent system: Ezetimibe were scanned in various hydrotropic agent in the spectrum mode over the UV range (200-400) and 2M Ammonium Acetate: 2M Sod. Citrate (1:1) was foundto be most appropriate because:

- Both drugs are soluble in it.
- Both drugs are stable in it.
- Both drugs exhibit good spectral characteristics in it.
- 2M Ammonium Acetate: 2M Sod. Citrate solutions have no interference with the λ_{max} of both drugs.

- More than 15 folds solubility enhancement.

Establishment of stability profile: Stability of both drugs was observed by dissolving Ezetimibe in 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution used as solvent, Solution of Ezetimibe wasprepared in the conc. of 5µg/ml and 10µg/ml respectively and scanned under timescan for 30 min. Spectra of both drugs under time scan shows that of both drugs arestable in mixed hydrotropic solution.

Linearity range and calibration graph: Standard stock solutions and different Aliquots were prepared using serial dilution method in hydrotropic solution 2M Ammonium Acetate: 2M Sod. Citrate (1:1).

Selection of wavelength for linearity

Solution of 10µg/ml Ezetimibe were prepared separately the solutions were scannedin the spectrum mode from 200 nm to 400 nm. The maximum absorbance of Ezetimibe was observed at 244.0 nm respectively. Ezetimibe showed linearity in theconcentration range of 10-50 µg/ml Calibration curve was plotted, absorbance versus concentration. To study the linearity of Ezetimibe the selected wavelength is: λ_{max} = 244.0 nm.

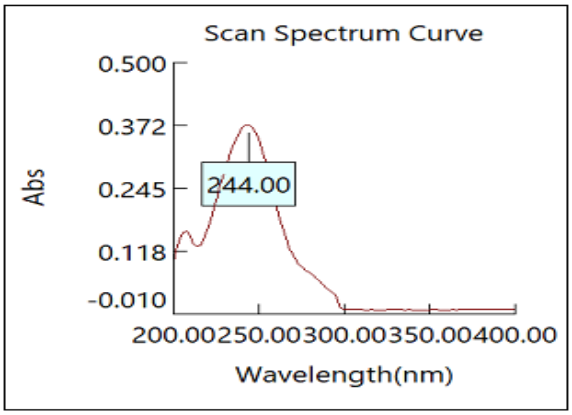

Figure 6.2: Determination of λ_{max} of Ezetimibe.

Table 6.5: Linearity of Ezetimibe at λ_{max} = 244.0 nm.

Standard Conc. (µg/ml)	Rep-1	Rep-2	Rep-3	Rep-4	Rep-5	Mean	S.D.	% RSD
0	0	0	0	0	0	0	0	0
10	0.145	0.146	0.147	0.144	0.143	0.145	0.001	0.975
20	0.285	0.284	0.287	0.286	0.287	0.285	0.001	0.408
30	0.432	0.433	0.435	0.432	0.434	0.433	0.001	0.269
40	0.578	0.579	0.577	0.579	0.581	0.578	0.001	0.229
50	0.719	0.718	0.719	0.718	0.716	0.718	0.001	0.153

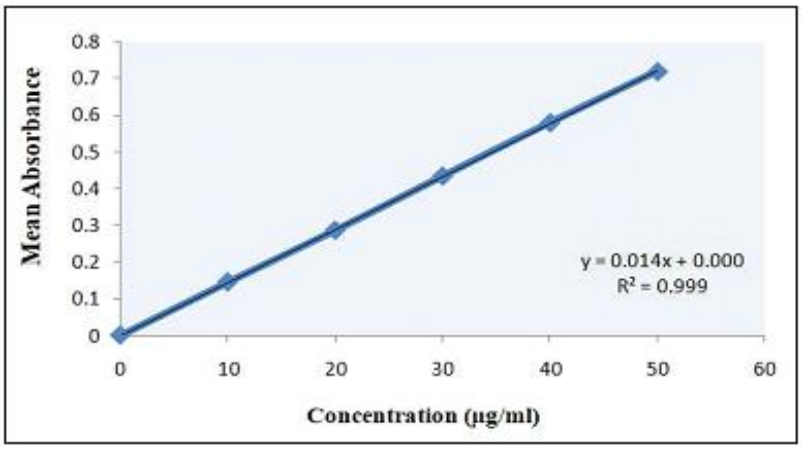

Figure 6.3: Calibration Curve of Ezetimibe.

Validation of simultaneous equation method

A_1: Linearity: Linearity of both drugs was established by response ratios of drugs. Response ratio of drug calculated by dividing the absorbance with respective concentration. Then agraph was plotted between concentration and response ratio.

Table 6.6: Response Ratio of Ezetimibe.

S. No.	Ezetimibe		
	Conc. (µg/ml)	ABS	Response Ratio
1	10	0.145	0.014
2	20	0.285	0.014
3	30	0.433	0.014
4	40	0.578	0.014
5	50	0.718	0.014

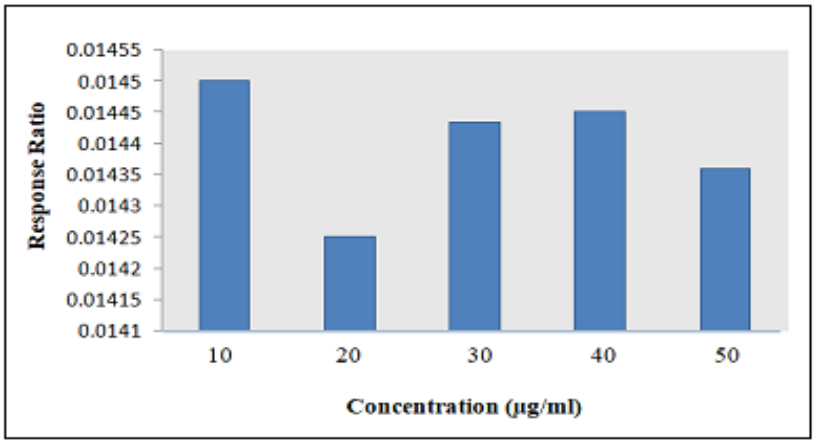

Figure 6.4: Graph of Response ratio graph for linearity for Ezetimibe B_1: Accuracy.

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100%, 120%. The recovery studies were carried out by adding

known amount of standard solution of Ezetimibe to preanalysed tablet powder. The resulting solutions were then re-analysed by proposed methods. Whole analysis procedure was repeated to find out the recovery of the added drug sample. This recovery analysis was repeated at 3 replicate of 5 concentrations levels.

Table 6.7: Recovery study of Ezetimibe (EZB) (80% level).

EZB tablet (mg)	Std. EZB Added (mg)	Rep-1		Rep-2		Rep-3		EZB % Mean
		EZB Found	% Found	EZB Found	% Found	EZB Found	% Found	
10	**8**	7.92	99.00	7.95	99.38	7.85	98.13	98.83
20	**16**	15.85	99.06	15.82	98.88	15.65	97.81	98.58
30	**24**	23.74	98.92	23.87	99.46	23.84	99.33	99.24
40	**32**	31.65	98.91	31.69	99.03	31.74	99.19	99.04
50	**40**	39.98	99.95	39.1	97.75	39.85	99.63	99.11
							Mean*	98.96
							SD*	0.256
							% RSD*	0.259

*Mean of 3 replicate and 5 concentrations

Table 6.8: Recovery study of Ezetimibe (100% level).

EZB tablet (mg)	Std. EZB Added (mg)	Rep-1		Rep-2		Rep-3		EZB % Mean
		EZB Found	% Found	EZB Found	% Found	EZB Found	% Found	
10	**10**	9.98	99.80	9.85	98.50	10.01	100.10	99.47
20	**20**	19.85	99.25	19.65	98.25	19.96	99.80	99.10
30	**30**	29.78	99.27	29.87	99.57	29.45	98.17	99.00
40	**40**	39.82	99.55	39.65	99.13	39.65	99.13	99.27
50	**50**	49.85	99.70	49.77	99.54	49.75	99.50	99.58
							Mean*	99.28
							SD*	0.243
							% RSD*	0.245

*Mean of 3 replicate and 5 concentrations

Table 6.9: Recovery study of Ezetimibe (120% level).

EZB tablet (mg)	Std.EZB Added (mg)	Rep-1		Rep-2		Rep-3		EZB % Mean
		EZB Found	% Found	EZB Found	% Found	EZB Found	% Found	
10	**12**	11.85	98.75	11.65	97.08	11.74	97.83	97.89
20	**24**	23.65	98.54	23.85	99.38	23.65	98.54	98.82
30	**36**	35.74	99.28	35.74	99.28	35.12	97.56	98.70
40	**48**	47.95	99.90	47.95	99.90	47.05	98.02	99.27
50	**60**	59.98	99.97	59.68	99.47	58.98	98.30	99.24

	Mean*	98.79
	SD*	0.561
	% RSD*	0.568

*Mean of 3 replicate and 5 concentration

C_1: Precision: Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility. Repeatability wasperformed by analyzing same concentration of drugs for five times. Day to Day wasperformed by analyzing 5 different concentration of the drug for three days in a week. The results are shown in tables 6.10-6.12.

C_1-1: Repeatability

Table 6.10: Repeatability of Ezetimibe.

Replicate	Concentration Found					
	10	**20**	**30**	**40**	**50**	
Replicate-1	9.85	19.85	29.85	39.78	49.78	
Replicate-2	9.75	19.74	29.78	39.85	49.96	
Replicate-3	9.92	19.65	29.65	39.65	49.78	
Replicate-4	9.78	19.82	29.74	39.78	49.12	
Replicate-5	9.72	19.65	29.65	39.65	49.65	
Mean	9.80	19.74	29.73	39.74	49.66	
% Mean	98.04	98.71	99.11	99.36	99.32	**98.91**
S.D.	0.081	0.093	0.086	0.089	0.320	**0.134**
% R.S.D.	0.808	0.466	0.287	0.222	0.641	**0.485**

C_1-2.1: Day-to-Day Variation

Table 6.11: Day-to-Day Variation of Ezetimibe.

Replicate	Concentration Found					
	10	**20**	**30**	**40**	**50**	
Day – 1	9.85	19.85	29.98	39.78	49.95	
Day – 2	9.78	19.78	29.65	39.65	49.65	
Day – 3	9.65	19.65	29.74	39.87	49.78	
Mean	9.76	19.84	29.8	39.86	49.84	
% Mean	97.6	99.20	99.33	99.65	99.68	**98.70**
S.D.	0.101	0.101	0.171	0.111	0.150	**0.263**
% R.S.D.	0.104	0.102	0.172	0.111	0.151	**0.863**

C_1-2.2: Analyst to analyst variation

Table 6.12: Analyst-to-Analyst Variation of Ezetimibe.

Replicate	Concentration Found					
	10	**20**	**30**	**40**	**50**	
Analyst -1	9.95	19.85	29.65	39.65	49.85	
Analyst -2	9.65	19.78	29.87	39.78	49.75	

Mean	9.80	19.82	29.76	39.72	49.80	
% Mean	98.00	99.08	99.20	99.29	99.60	**99.03**
S.D.	0.212	0.049	0.156	0.092	0.071	**0.116**
% R.S.D.	2.121	0.247	0.519	0.230	0.141	**0.652**

C_1-3: Reproducibility

Table 6.13: Reproducibility of Ezetimibe.

Replicate	Concentration Found					
	10	**20**	**30**	**40**	**50**	
Replicate-1	9.85	19.65	29.96	39.65	49.85	
Replicate-2	9.65	19.74	29.85	39.85	48.95	
Replicate-3	9.75	19.65	29.74	39.65	48.78	
Replicate-4	9.65	19.65	29.65	39.78	48.65	
Replicate-5	9.85	19.85	28.95	39.65	48.71	
Mean	9.75	19.71	29.63	39.72	48.99	
% Mean	97.50	98.54	98.77	99.29	97.98	**98.41**
S.D.	0.100	0.088	0.398	0.094	0.495	**0.235**
% R.S.D.	1.000	0.442	1.325	0.234	0.990	**0.798**

Analysis of tablet sample

Twenty marketed tablets of Ezetimibe were weighed and ground to a fine powder; amount equal to 10mg of Ezetimibe was taken in 10 ml volumetric flask. Then 8 ml of 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution was added and the flask was sonicated for about 10 min to solubilize the drug present in tablet powder and the volume was made up to the mark with hydrotropic solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with RO Water to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from calibration curve method. The procedure was repeated for five times.

Table 6.14: Analysis of Tablet Formulation of Ezetimibe.

Drug	Labelclaim (mg)	Amountfound (mg)	Label claim(%)	S.D.	% RSD
Ezetimibe	10	9.85	98.50	0.123	0.256

RESULTS AND DISCUSSION

In the proposed method Ezetimibe estimated by hydrotropic phenomena. Till date there is no method for the spectrophotometric estimation of Ezetimibe by using dye drug reaction. Following marketed formulation to be estimated by using dye drug reaction. The developed methods were found to be linear. The values of mean percent recoveries were found to shown in Table 5.6 and results of validationwere shown in Table 7.2 to 7.4.

The mean percent label claims of tablets by the proposed methods were close to 100, indicating the accuracy of the proposed method and low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method.

Table 7.1: Results of Linearity of Ezetimibe.

Parameter	Ezetimibe
Working λ_{max}	244.0 nm
Beer's law limit (µg/ml)	10-50
Correlation Coefficient (r^2)*	0.999
Slope (m)*	0.012
Intercept (c)*	0.008

Table 7.2: Results of Recovery Studies on Marketed Formulations.

Recovery Level %	% Recovery (Mean ± SD)* Ezetimibe
80	98.96 ± 0.256
100	99.28 ± 0.243
120	98.79 ± 0.568

Table 7.3: Results of validation (Mean ± SD)*

Parameter		Method
Precision*	Repeatability	98.91 ± 0.134
	Day-to-Day	98.70 ± 0.263
	Analyst-to-Analyst	99.03 ± 0.116
	Reproducibility	98.41 ± 0.235

*Average of five determination

Table 7.4: Analysis of Tablet Formulation.

Drug	Labelclaim (mg)	Amount Found (mg)	Label claim(%)	S.D.	% RSD
Ezetimibe	10	9.85	98.50	0.123	0.256

CONCLUSION

Modern medicines for human use are required to comply with specific standards and regulation set forth by the concerned authorities. The efficacy and safety of medicinal products can only be assured by analytical monitoring of its quality. Pharmaceutical analysis is an art and science of determining the concentration of drug constituents present in marketed formulation. It is considered as an applicationof procedures necessary to determine and estimate the identity, strength, quality andpurity of drug. Therefore, the quality control laboratory is considered as the backbone of the pharma industries with ever-increasing need for the development of analytical techniques for drug formulation. The methods were developed by experimentation based on thorough literature survey

and ascertained by statistical parameters of sampling. The simplicity, rapidity, reproducibility and economy of the proposed methods completely fulfill the objective of this research work. The entire UV work was performed on Labindia UV/Vis double beam-double detector spectrophotometer (3000 plus) used for conduct chromatographic method development.

The ability to increase the aqueous solubility can be a valuable aid for increasing the efficacy and/or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility of poorly soluble drugs. Complexation, Use of co-solvents, Alteration of pH, Use of surfactants, Supercritical fluid re-crystallization, Micronization, Solid dispersion, Eutectic mixture, Hydrotropic solubalisation, Mixed hydrotropic solubalisation, Mixed solvency. The above mentioned methods have been used widely in various fields of pharmacy. However, applications of 'Mixed Hydrotropic Solubilization' and 'Mixed Solvency' have not been explored to appreciable extent in various fields of pharmacy. The significance of study is to improve the aqueous solubility of Ezetimibe and enhance its efficacy and reduces its side effects by using hydrotropicagents.

In conclusion the developed methods were found simple, sensitive and economical for the simultaneous estimation of selected active pharmaceutical ingredients in their tablet formulation. Validation of developed methods was performed according to ICH guidelines. The standard deviation, % RSD for the methods are low, reflecting a high degree of precision of the methods. The results of the recovery studies performed show the high degree of accuracy of the proposed methods. The advantage of method was found being simple, economic, rapid and subsequently not required sophisticated technique, instrument and costly solvents. Thus, the proposedmethods can be successfully applied for determination and dissolution testing of selected drugs in commercial formulation.

CONFLICTS OF INTERESTS

There are no conflicts of interests.

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