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Research Article

DEVELOPMENT AND VALIDATION OF STABILITY INDICATING UV SPECTROPHOTOMETRIC SIMULTANEOUS EQUATION METHOD FOR DETERMINATION OF EZETIMIBE AND GLIMEPIRIDE IN BULK DRUGS AND MARKETED FORMULATION

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ABSTRACT

Ezetimibe and Glimepiride used as Anti - hypercholesterolemia drugs. A simple , specific, accurate and precise stability indicating UV spectroscopy method has been developed and validated for simultaneous determination of Ezetimibe and Glimepiride in bulk drugs and marketed formulation (tablets). The developed method involves solving of simultaneous equations (Vierodt's method) using methanol as solvent where absorbance maxima λ max for GLIM and EZET was found to be at 226nm and 233nm respectively. Both the drugs obeyed Beer's law in the concentration range of 10- 30 µg/ ml & 1 – 3 µg/ ml. The method was validated as per ICH guidelines values of correlation coefficients (r2) 0.99 indicated good linearity of Calibration curve for both the drugs. The recovery of GLIM and EZET from the standard mixture solution was 99.65% and 100.3% respectively. The developed method was found to be accurate, reliable robust showing LOD 2.64 µg/ml (GLIM) and 26.4 µg/ml (EZET) and LOQ 8 µg/ml (GLIM) and 80 µg/ml(EZET) . Forced degradation was also performed the obtained spectra doesn't show any degradation products under any stress conditions applied. Hence the method developed is stability indicating and can be used for estimation of EZET and GLIM in routine lab analysis.

Keywords: Simultaneous Estimation, UV spectroscopy, EZET – Ezetimibe, GLIM –Glimepiride & FD – Forced Degradation.

INTRODUCTION

Ezetimibe (EZET) is an anti-hyperlipidemic medication used to lower cholesterol levels. It is chemically (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-onewith chemical formula C24H21F2NO3 .It is white amorphous powder which is freely soluble in methanol, Acetonitrile and practically insoluble in water. Its melting point is 163oC. Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with hypercholesterolemia, >90% bound to human plasma protein. In humans, Ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Route of elimination 78% of the dose is excreted into feces. 11% of the dose is excreted into urine, half life is 22 hrs toxicity caused are arthralgia (0.3%), dizziness (0.2%), and gamma-glutamyl transferase increase (0.2%).

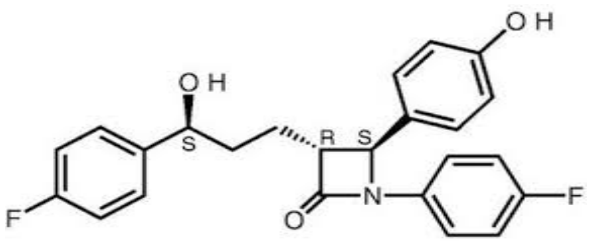

Figure 1. Structure of Ezetimibe

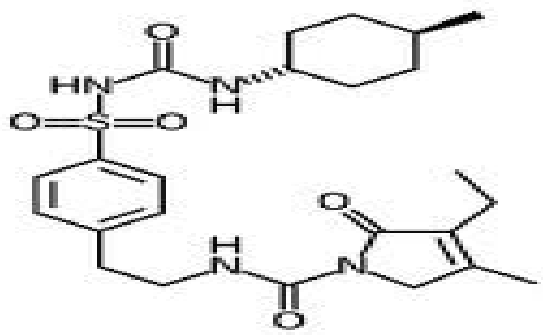

Figure 2. Structure of Glimepiride

Glimepiride (GLIM) is a medium- to long-acting sulfonylurea antidiabetic drug with IUPAC name3-ethyl-4-methyl-N-{2-[4-({[(4-methylcyclohexyl) carbamoyl] amino} sulfonyl) phenyl] ethyl} -2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide and chemical formula C24H34N4O5S, freely soluble in DMSO ,Methanol with melting point 207 oC Glimepiride, like glyburide and glipizide, is a "second-generation" sulfonylurea agents. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin. Half life approx 5 hours following single dose toxicities caused due to GLIM are hypoglycemic reactions with coma, seizures and other neurological impairment.

The combination of these two drugs is used for treatment of hypercholesterolemia. And the clinical studies showed good results in reducing cholesterol when these two drugs are used in combination

As per literature review Ezetimibe in combination with Glimepiride is not official in any pharmacopeia. Several Analytical methods like RP-HPLC, HPTLC, UPLC, UV-Spectroscopy has been reported on individual drugs and in combination with other drugs. But stability indicating UV spectroscopy method has not been reported till now on combination of these two drugs. Hence this combination has been selected to carry out the present research work.

The objective of the present work is to develop a simple, precise, robust stability indicating Uv spectrophotometric method for estimation of Ezetimibe and Glimepiride in bulk drug and marketed formulation and validate it as per ICH guidelines and perform stress studies on developed method to prove stability of drug under stress conditions which in turn helps to assess shelf life of the drug product.

MATERIALS AND METHODS

Chemicals and Reagents

Ezetimibe and Glimepiride standard drugs obtained as Gift samples from Pegasus Farmaco India pvt Ltd showing 99.88 %, 99.91% potency. The marketed preparation (tablets) obtained from local pharmacy with brand name EZIWA with label claim EZET (10mg) + GLIM (1mg) manufacturer Kaytross health care limited Mumbai. All the chemicals and reagents used are of analytical grade.

Instrumentation

UV double beam spectrophotometer - PG Instrumentations ltd. Model no. 60 consisting of fixed slit width of 2 nm & 1 cm quartz cells was used. Electronic balance of Wensar weighing scales Model PGB-600, volumetric glassware was used of class A.

Solubility studies of drug: Proper wavelength selection of method depends upon the nature of sample and its solubility. 1mg of standard drug sample was taken and its solubility was checked in various solvents like Distill water, Acetonitrile, methanol, 0.1N HCl, Phosphate Buffer, Acetone, this studies are carried out at 25 ± 2 0 C.

PREPARATION OF STANDARD STOCK SOLUTIONS

a) Preparation of EZET standard stock solution (1000 µg/ml):

Accurately weighed 100mg of Pure EZET (API) was taken in a 100ml of volumetric flask , dissolved in methanol and made up to the mark to get a concentration of 1000µ g/ml. from above stock solution 0.2ml was transferred into 10 ml volumetric flask and diluted to 10ml with methanol to get a concentration of 20µ g/ml it was taken as working standard concentration.

b) Preparation of GLIM standard stock solution (100µ g/ml):

Accurately weighed 10mg of Pure GLIM (API) was taken and dissolved in 100ml of diluent in a 100ml of volumetric flask to get a concentration of 100µ g/ml. from above stack solution 0.2ml was transferred into 10ml Volumetric flask and diluted to 10ml with methanol to get a concentration of 2 µ g/ml it was taken as working standard concentration.

Procedure for selection of wave length:

2ml of working standard solution of Ezetimibe (100µg/ml) and Glimepiride (10µg/ml) was transferred into two 10ml volumetric flasks separately and diluted to 10ml with

methanol to get 20µ g/ml of EZET and 2µ g/ml of GLIM. These two solutions were taken and scanned between 200nm to 400nm on scan/spectrum mode using methanol as blank. As per spectra recorded GLIM shows λ max at 226nm (λ1) and EZET shows λ max at 233nm (λ2) and respectively.

Plotting of calibration curve:

The calibration curves were plotted over a concentration range of 1-15 µg/ml for Glimepiride and Ezetimibe. Accurately measured standard solutions of Glimepiride and Ezetimibe (1, 1.5, 2, 2.5,3 ml) were transferred to a series of 10 ml of volumetric flask and diluted to the mark with methanol. The absorbances of the both solutions (EZET & GLIM) were measured at both wavelengths i.e. 226 nm and 233 nm against methanol as blank. Calibration curve was plotted at both wavelengths and two equations were solved using the absorptivity values obtained from the absorbance values of calibration curve.

VALIDATION PROCEDURE

It was performed as per ICH guidelines specificity. The solutions of mixed standard solution consisting EZET (20mcg/ml) and GLIM (2mcg/ml) , sample (tablet) solution were prepared and spectra was recorded for both and compared with each other .Both spectra shows peaks at 226nm and 233nm for GLIM and EZET respectively.

Linearity and range:

The linear response of samples was determined over a five concentration range of 50-150 %. Accurately measured standard solutions of EZET & GLIM (1, 1.5, 2, 2.5, 3 ml) were transferred to a series of 10 ml of volumetric flask and diluted up to the mark with methanol. The absorbances of the solutions were measured at 228 nm and 233 nm against methanol as blank. The calibration curve of absorbance vs. respective concentration was plotted and correlation coefficient (r2) and regression line equations for EZET and GLIM calculated.

Accuracy:

Accuracy is determined by calculating percentage recovery, recovery studies is carried by standard addition method where to the formulation (pre analyzed sample), the reference standards of the EZET and GLIM were added at three concentration level of 75%, 100%, 125% of assay conc and recovery studies were carried out three times and the percentage recovery and percentage mean recovery were calculated for drug.

Precision:

a)System precision: The variation of results on same day analysed by actual determination of absorbance of fixed concentration of the standard preparation(API) consisting of 20µ g/ml for EZET and 2µ g/ml. of GLIM for six times on the same day wwithin the Beer's range and Finding out the absorbance at two wave length..

b)Method precision: Variation of results on same day analysed by actual determination of absorbance fixed concentration of the sample (Tablet) preparation consisting of 20µ g/ml for EZET and 2µ g/ml. of GLIM for six times on same day within the Beer's range and finding out the absorbance at two wave lengths.

Acceptance criteria:

%RSD should not be more than NMT 2.0% as per ICH guide lines

Limit of detection (LOD) & Limit of quantification (LOQ):

LOD &LOQ was calculated by taking the slope and standard deviation of response from calibration curve of analyte which it used to determine linearity. It is calculated as

$LOD = 3.3\sigma/S$ $LOQ = 10\sigma/S$

Where, σ = the standard deviation of the response

S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte.

Robustness: To demonstrate the robustness of the method, prepared solution as per test method and absorbance was checked at variable conditions like using different wavelength λmax (max ± 1 nm)

Ruggedness: The ruggedness of the method was studied by the determining the analyst to analyst variation by performing the Assay by two different analysts under same operational and environmental conditions.

System suitability: Standard solutions consisting EZET 20mcg/ml & GLIM 2mcg/ml were prepared and absorbance was checked at 226nm and 233nm for six times. The system suitability parameters like absorbance, Mean, SD, %RSD factor were evaluated.

Estimation of Ezet and Glim in tablet formulation: (assay)

From calibration curve the concentration 100% is selected to perform assay.

Preparation of test solution with tablets: 10 tablets were weighed and powdered tablet equivalent to 100mg EZETIMIBE and 10mg GLIMEPIRIDE was weighed and taken into 100ml volumetric flask then 50ml methanol was added and shaken well to dissolve tablet powder completely and volume was made up to mark with diluent then solution as sonicated for about 20min and filtered with 0.45 µ whattman filter paper to remove particles if any. From the above stock solution 1ml of solution was withdrawn and taken in 10ml volumetric flask and volume was made up to mark with diluent. From this again the further dilution were prepared to obtain concentration of 20µ g/ml for EZET and 2µ g/ml. of GLIM. The concentration of EZET and GLIM was obtained from simultaneous equation.

CALCULATION:

For calculating assay simultaneous equation has been used here

$$Cx = \frac{(A2\ ay1 - A1\ ay2)}{(ax2\ ay1 - ax1\ ay2)}$$

$$Cy = \frac{(A1\ ax2 - A2\ ax1)}{(ax2\ ay1 - ax1\ ay2)}$$

Where: A1, A2 are absorbance of Formulation at 226 nm and 233nm , ax1 and ax2 are absorptivity of GLIM at 226 nm and 233 nm , ay1 and ay2 are absorptivity of EZET at 226 nm and 233 nm , Cx and Cy are concentrations of EZET and GLIM respectively.

Forced degradation studies:

Forced degradation studies are performed to prove the stability indicating property of the method.

1. Acid hydrolysis: Solution for acid degradation studies were prepared in methanol (20µg/ml of EZET and 2 µg/ml of GLIM) and add to it 1 ml 0.1 N HCl at room temperature (22°C) for 3 h of the sample preparation, therefore the sample was neutralized with 0.1 N base and analyzed at 226 nm and 233 nm of EZET and GLIM respectively taking mixture of 1 ml acid + 1 ml base diluted to 10 ml with methanol as blank.

2. Alkaline hydrolysis: Solution for base degradation studies were prepared in methanol (20 µg/ml of EZET and 2µg/ml of GLIM) and to it add 1ml 0.1 N NaOH and kept at room temperature (22°C) for 3 hrs and the resultant the sample was neutralized with 0.1 N acid and analyzed at 226 nm and 233 nm of EZET and GLIM respectively taking mixture of 1 ml acid + 1 ml base diluted to 10 ml with methanol as blank

3. Thermal degradation: Fifty mg drug was weighed and kept in the oven and temperature was maintained at 80°C for 3 h, after that the solutions for photostability studies were prepared in methanol and the dilution (20 µg/ml of EZET and 2 µg/ml of GLIM) were prepared and analyzed in UV spectrophotometer at 226 nm and 233 nm of EZET and GLIM respectively.

4. Photolytic degradation: Fifty mg drug was weighed and kept in the UV chamber for 3 hrs at 365 nm wavelength, after that the solutions for photostability studies were prepared in methanol and the dilutions (20µg/ml of EZET and 2 µg/ml of GLIM) were prepared & analyzed in UV spectrophotometer at 226 nm and 233 nm of EZET and GLIM respectively

5. Oxidation degradation (3%) H2O2: Solution for oxidative degradation studies were prepared in methanol (20 µg/ml of EZET and 2µg/ml of GLIM) and 1 ml 3% H2O2 solution and kept at room temperature (22°C) and the resultant solutions analyzed 15 min after preparation at 226 nm and 233 nm of EZET and GLIM respectively.

Record the absorbance of stressed samples then compare it with absorbance of unstressed sample to determine the % degradation.

$$\% \text{ degradation} = \frac{(\text{Response of unstressed sample}) - (\text{response of stressed sample})}{\text{Response of unstressed sample}} \times 100$$

RESULTS AND DISCUSSION:

Solubility studies: various solvents like Acetonitrile, methanol, phosphate buffer etc were used to determine the solubility of Ezetimibe and Glimepiride. Among all these solvents it was found that both drugs showed excellent

Table : 1 Calibration curve of ezetimibe

parameters		Ezetimibe	Glimepiride
1	Diluent / solvent	methanol	methanol
2	Absorption maximum (λ max)	233nm	226nm
3	Working standard concentration	20 µg/ml	2 µg/ml

Table : 2 Linearity of glimepiride at two wave lengths

Conc mcg/ml	Abs at 226nm λ1	Abs at 233nm λ2
1	0.111	0.0845
1.5	0.168	0.128
2	0.223	0.169
2.5	0.278	0.213
3	0.333	0.255
MEAN	0.2226	0.1699
SLOPE	0.1108	0.0852
CORRELATION COEFF	0.999973935	0.99995592

Table : 3 Linearity of Ezetimibe at two wave lengths

Conc mcg/ml	Abs at 233nm (λ1)	Abs at 226nm (λ2)
10	0.397	0.186
15	0.596	0.279
20	0.793	0.373
25	0.993	0.466
30	1.189	0.559
MEAN	0.7936	0.3726
SLOPE	0.03962	0.118
CORRELATION COEFFICIENT	0.99999605	0.999977982

Table : 4 Linearity data of EZET+GLIM

mcg/ml	Abs at 226nm	Abs at 233nm
50	0.112	0.398
75	0.167	0.595
100	0.224	0.796
125	0.277	0.995
150	0.332	1.188
MEAN	0.2224	0.7944
SLOPE	0.011	0.03976
CORRELATION COEFF	0.999947112	0.999978064

Data Associated with Method Validation

Table : 5 Linearity of ezetimibe

S. No.	Conc (µg/ml)	Abs at 233nm
1	10	0.397
2	15	0.596
3	20	0.793
4	25	0.993
5	30	1.189
MEAN		**0.7936**
SLOPE		**0.039**
CORRELATION COEFF		**0.999973935**

Table : 6 linearity of glimepiride

S.no.	Conc(µg/ml)	Abs at 226nm
1	1	0.111
2	1.5	0.168
3	2	0.223
4	2.5	0.278
5	3	0.333
MEAN		**0.223**
SLOPE		**0.118**
CORRELATION COEFF		**0.99999605**

Table : 7 Linearity and Range of EZET and GLIM

parameter	EZET at 233nm	EZET at 226nm	GLIM at 233nm	GLIM at 226nm	EZET + GLIM 233nm	EZET + GLIM 226nm
Beer's lamberts law (range)	**10-30 mcg/ml**	**10-30 mcg/ml**	**1-3 mcg/ml**	**1-3 mcg/ml**	**50 -150 mcg/ml**	
Mean abs	**0.793**	**0.372**	**0.223**	**0.169**	**0.792**	**0.221**
slope	**0.03962**	**0.118**	**0.110**	**0.0852**	**0.011**	**0.03976**
Correlation coefficient	**0.999**	**0.999**	**0.99**	**0.99**	**0.99**	**0.99**

Table : 8 Data of recovery studies

Recovery level	Abs of Std 226nm GLIM	Abs of Std 233nm EZET
75%	**0.224**	**0.793**
100%	**0.227**	**0.993**
125%	**0.334**	**1.81**

Table : 9 Accuracy

Level of Addition	Drug	Amount taken (µg/ml)	Mean of sample abs at 223& 226nm	Amount in Added (µg/ml)	Total Conc µg/ml	Amount Recovered µg/ml	% recovered	%average recovery
75%	GLIM	0.5	0.223	1.5	2	1.99	99.55%	99.65% For GLIM
	EZET		0.793		20	19.99	99.99%	
100%	GLIM	0.5	0.277	2	2.5	2.5	100%	
	EZET		0.992		25	24.97	99.98%	100.3% For EZET
125%	GLIM	0.5	0.332	2.5	3.0	2.98	99.4%	
	EZET		1.182		30	30.03	101%	

Precision studies

Table : 10 System precision

SYSTEM PRECISION Of GLIMEPIRIDE			SYSTEM PRECISION OF EZETIMIBE	
Sample	**Abs at 226nm**	**Abs at 233nm**	**Abs at 226nm**	**Abs at 233nm**
Replicate -1	0.223	0.171	0.373	0.795
Replicate -2	0.223	0.172	0.373	0.795
Replicate -3	0.223	0.171	0.373	0.796
Replicate -4	0.223	0.173	0.372	0.795
Replicate -5	0.221	0.171	0.373	0.795
Replicate -6	0.221	0.171	0.373	0.796
Mean	**0.2223**	**0.1715**	**0.373**	**0.1715**
SD	**0.001**	**0.001**	**0.00041**	**0.001**
% RDS	**0.46**	**0.49**	**0.11**	**0.49**

Table : 11 Method precision

METHOD PRECISION OF Ezetimibe 10mg/ml + Glimepiride 1 mg/ml		
S. No.	**ABS at 226nm**	**Abs at 233nm**
1	0.224	0.795
2	0.224	0.796
3	0.223	0.795
4	0.224	0.795
5	0.224	0.796
6	0.223	0.795
MEAN	0.224	0.795
SD	0.0005	0.001
%RSD	**0.23**	**0.06**

Table : 12 LOD & LOQ

PARAMETER	GLIMEPIRIDE at 226mn	EZETIMIBE at 233nm
MEAN	0.223	0.794
SD	0.088	0.313
SLOPE	0.11	0.039
LOD	2.64 **µg/ml**	26.4 **µg/ml**
LOQ	8 **µg/ml**	80 **µg/ml**

ROBUSTNESS

Table : 13 Robustness of GLIM

S. No	225nm	226nm	227nm
1	0.221	0.224	0.226
2	0.220	0.224	0.226
3	0.221	0.223	0.227
4	0.221	0.224	0.226
5	0.221	0.224	0.226
6	0.222	0.223	0.226
AVG	**0.221**	**0.224**	**0.226**
SD	**0.001**	**0.001**	**0.000**
%RSD	**0.29**	**0.23**	**0.18**

Precision studies

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SYSTEM PRECISION Of GLIMEPIRIDE			SYSTEM PRECISION OF EZETIMIBE	
Sample	**Abs at 226nm**	**Abs at 233nm**	**Abs at 226nm**	**Abs at 233nm**
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Replicate -3	0.223	0.171	0.373	0.796
Replicate -4	0.223	0.173	0.372	0.795
Replicate -5	0.221	0.171	0.373	0.795
Replicate -6	0.221	0.171	0.373	0.796
Mean	**0.2223**	**0.1715**	**0.373**	**0.1715**
SD	**0.001**	**0.001**	**0.00041**	**0.001**
% RDS	**0.46**	**0.49**	**0.11**	**0.49**

Table : 11 Method precision

METHOD PRECISION OF Ezetimibe 10mg/ml + Glimepiride 1 mg/ml		
S. No.	**ABS at 226nm**	**Abs at 233nm**
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MEAN	0.224	0.795
SD	0.0005	0.001
%RSD	**0.23**	**0.06**

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MEAN	0.223	0.794
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LOD	2.64 **µg/ml**	26.4 **µg/ml**
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5	0.221	0.224	0.226
6	0.222	0.223	0.226
AVG	**0.221**	**0.224**	**0.226**
SD	**0.001**	**0.001**	**0.000**
%RSD	**0.29**	**0.23**	**0.18**

solubility in methanol. Hence methanol is selected as solvent for present investigation.

Selection of working wave length: From standard spectra of EZET and GLIM the absorbance maxima were obtained at 233 nm and at 226nm respectively. Hence 226nm is taken as working wavelength of GLIM and 233nm taken as working wavelength of EZET.

Method development: The method optimized, shows all the results as per requirement. The method optimized is simple, accurate and reproducible.

Plotting of calibration curve: The correlation coefficient for linear curve obtained between concentration vs. Absorbance of standard preparations of EZET and GLIM is 0.99 and 0.99 at 233nm and 226nm resp. shown in table no.07.

Specificity: The UV graphs obtained depicts there is no interference of excipients, solvent and placebo with the absorbance of analyte which indicate that the method is specific for the analysis of analytes in their dosage form show in Fig.no:11&12

Linearity and range: The obtained absorbance values were plotted taking Conc vs. absorbance. The obtained was linear and correlation was found to be 0.99 for both drugs. The relationship between the concentration and absorbance of EZET and GLIM is linear in the range examined since all points lie in a straight line and the correlation coefficient is within limits shown in table no .07.

Recovery studies: The percentage mean recovery of GLIM and EZET is 99.65% and 100.3 % respectively. Shown in table no. 10.

Precision: The %RSD of the results was found to be below 2 % shown in table no. 11 – 12.

LOD and LOQ: The LOD for this method was found to be 2.64µg/ml for GLIM and 26.4 µg/ml for EZET. LOQ for this method was found to be 8 µg/ml for GLIM and 80µg/ml for EZET shown in table no. 13

Robustness: The %RSD of GLIM and EZET at different wave length was within limits NMT 2.0.The method was found to be Robust even at different wave lengths shown in table no. 13 - 14

Ruggedness: The % RSD for assay was found to be below 2% shown in table no. 15 – 18.

System suitability: The % RSD for the Absorbance of EZET and GLIM from 6 sample replicates of each Standard solution was not more than 2.0 .%RSD for Ezetimibe was found to be 0.75 and for Glimepiride was found to be 0.07. shown in table.no.19

Tablet assay: The amount of GLIM and EZET present in the taken dosage form was found to be 0.95 mg and 10.0.5 mg respectively shown in table no: 20

Forced degradation studies: Both the drugs were found to be stable in stress condition shown in table.no,21

CONCLUSION

The developed UV spectroscopy method for the determination of Ezetimibe and Glimepiride was validated as per ICH guidelines. All the validation parameters like Specificity, accuracy, precision, linearity obtained results were within the limits and drug as found to be stable in all the stress conditions like Acid, Alkali, Thermal, Light and Peroxide. Hence from obtained data it is concluded that the developed method is simple, accurate, reliable, economic and it can be employed for routine quality control analysis of Ezetimibe and Glimepiride tablets in drug testing laboratories and pharmaceutical industries without any interference from excipients.

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