EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 7
66-73
Year: 2017

VALIDATION OF HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) METHOD FOR DETERMINATION OF TRIMETAZIDINE IN PHARMACEUTICAL DOSAGE FORMS

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Article Received on 03/05/2017 **Article Revised on 23/05/2017** **Article Accepted on 13/06/2017**

ABSTRACT

A stability-indicating HPLC method was validated for the determination trimetazidine in tablet dosage form. The chromatographic conditions comprised of a 250 X 4.6 mm column containing 5-µm; packing L1 (C18), with a mobile phase consisting of mix 40 volumes of buffer and 60 volumes of methanol (Pass the solution through 0.45µmembrane filter and degas) with flow rate of 1.0 ml/min. Detection was carried out at 240 nm. The retention time of trimetazidine was found to be 3.0 min. The linear regression analysis data for the calibration plots showed good linear relationship within the concentration range 0.070-0.280 µg/ml. The value of correlation coefficient was found to be 1.00. The recovery of trimetazidine hydrochloride was about 98–102%. Trimetazidine dihydrochloride was subjected to stress conditions including acidic, alkaline, oxidation, photolysis and thermal degradation. Trimetazidine is more sensitive to wards acidic degradation. The method was validated as per ICH guidelines.

KEYWORDS: Trimetazidine, HPLC.

INTRODUCTION

Trimetazidine is an anti-ischemic (anti-anginal) metabolic agent, which improves myocardial glucose utilization through inhibition of long-chain 3-ketoacyl CoA thiolase activity, which results in a reduction in fatty acid oxidation and a stimulation of glucose oxidation. High fatty acid oxidation rates are detrimental during ischemia due to an inhibition of glucose oxidation leading to uncoupling of glycolysis and an increase in proton production, which has the potential to accelerate sodium and calcium overload in the heart, which leads to an exacerbation of ischemic injury and decreased cardiac efficiency during reperfusion.[1,2]

Trimetazidine is chemically known as 2 [1-(2, 3, 4-trimethoxybenzyl)-piperazine dihydrochloride (Fig 1). The orally administered antianginal agent trimetazidine increases cell tolerance to ischaemia by maintaining cellular homeostasis.[3] To date, all analytical methods described in literature for the determination of trimetazidine in pharmaceutical dosage form and biological fluids involve spectrophotometric, high performance liquid chromatography, liquid chromatography–mass spectrometry methods and high performance thin layer chromatography.[4-8] In the present work, we validate a simple, precise, accurate, selective and robust liquid chromatographic method for the determination of Trimetazidine in pharmaceutical dosage form as an alternative methods.

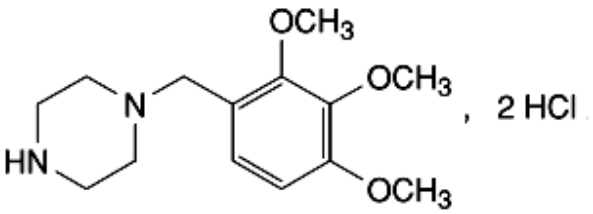


Fig 1: Chemical structure of trimetazidine dihydrochloride

MATERIALS AND METHODS

Procedure for the method of Assay

Diluent

Mix 10 volumes of methanol and 90 volumes of HPLC grade water.

Buffer Preparation

Dissolve 2.27 gm of potassium Dihydrogen Phosphater and 4.7 gm of Disodium hydrogen phosphate anhydrous

into a 1000 ml of HPLC grade water. adjust pH 2.8 with orthophosphoric acid.

Standard solution
Weigh accurately about 35.0 mg of Trimetazidine Hydrochloride working standard (Reference Standard) into a 200 ml volumetric flask. Dissolve and dilute to volume with diluent. Finally filter the solution through 0.45 µ membrane filter.

Sample solution
Weigh accurately 20 tablets and calculate the average weight of them. Crash the tablets into fine powder. Take about 309.0 mg powder (equivalent to 35 mg of Trimetazidine Hydrochloride) into a 200 ml volumetric flask, add 120 ml of diluent sonicate for 35 minutes with gentle shake and dilute upto mark with diluent,mix and Filter the solution through whatman filter paper. Finally filter the solution through 0.45 µ membrane filter.

Typical HPLC conditions
Column: 250 X4.6 mm column containing 5-µm; packing L1 (C18)
Mobile phase: Mix 40 volumes of buffer and 60 volumes of methanol. Pass the solution through 0.45µmembrane filter and degas.
Flow rate : 1.0 ml/ minute
Injection volume : 20 µl
Wavelength : 240 nm
Column Temperature : 30°C

Procedure
Inject 20 µl of standard solution one after another until the relative standard deviation for replicate injections is not more than 2%. Inject the sample solution and obtain the chromatograms for the standard and the sample solution.

Calculation
Content of Trimetazidine Hydrochloride / Tablet

$$= \frac{A_S \times W_{Std.} \times 200 \times P_{Std.} \times A_{WT}}{A_{Std.} \times 200 \times W_S \times 100} \text{ mg}$$

Where,
A_S = Peak area due to Sample Preparation
W_{Std} = Weight taken of Working Standard in mg
$P_{Std.}$ = Potency of Working Standard in percentage
A_{WT} = Average weight of tablets
$A_{Std.}$ = Peak area due to Standard Preparation
W_S = Weight taken of sample in mg

METHODS VALIDATION AND OBSERVATIONS

Specificity (Stability Indicating)
Peak Purity
Using the PDA detector and one of the spiked samples prepared in 7.0, determine the peak Purity index and single point threshold, for the Trimetazidine Hydrochloride peak.

Acceptance Criteria
The peak purity index is greater than single point threshold. so as to confirm peak identity.

Observation

Peak	Area	Peak purity index	Single point threshold
Trimetazidine Hydrochloride	2123359	0.999996	0.999948

Remarks: The Trimetazidine Hydrochloride peak complies with the acceptance criteria.

Forced Degradation
Prepare a series of sample solutions and deliberately degrade as follows:

Acidic Degradation: (2M HCl)
Sample preparation
From 20 tablets, determine the average weight and crush the tablet into fine powder and take a quantity of powder about 780.0 mg (equivalent to 87.5 mg of Trimetazidine Hydrochloride) in a 100 ml volumetric flask. Add about 10 ml 2M HCl, with gentle shake and mix for 1 hour dilute upto mark with Diluent. Filter the solution through Whatman filter paper. Dilute 5 ml of this solution to 25 ml with Diluent. Finally filter the solution with 0.45µ disc filter.

Basic Degradation: (2M NaOH)
Sample preparation
From 20 tablets, determine the average weight and crush the tablet into fine powder and take a quantity of powder about 780.0 mg (equivalent to 87.5 mg of Trimetazidine Hydrochloride) in a 100 ml volumetric flask. Add about 10 ml 2M NaOH, with gentle shake and mix for 1 hour dilute upto mark with Diluent. Filter the solution through Whatman filter paper. Dilute 5 ml of this solution to 25 ml with Diluent. Finally filter the solution with 0.45µ disc filter.

Heat Degradation
Sample preparation
From 20 tablets, determine the average weight and crush the tablet into fine powder and take a quantity of powder about 780.0 mg (equivalent to 87.5 mg of Trimetazidine Hydrochloride) in a 100 ml volumetric flask. Add about 60 ml Diluent with gentle shake and mix volume upto mark with Diluent in an air oven at105^{0}C for 1 hour. Filter the solution through Whatman filter paper. Dilute 5 ml of this solution to 25 ml with Diluent. Finally filter the solution with 0.45µ disc filter.

Light Degradation
Sample preparation
From 20 tablets, determine the average weight and crush the tablet into fine powder and take a quantity of powder about 780.0 mg (equivalent to 87.5 mg of Trimetazidine Hydrochloride) in a 100 ml volumetric flask. Add about

60 ml Diluent with gentle shake and mix volume upto mark with Diluent.This sample solution to store light(under a lamp) for a 24 hours. Filter the solution through Whatman filter paper. Dilute 5 ml of this solution to 25 ml with Diluent. Finally filter the solution with 0.45µ disc filter.

Acceptance Criteria

The peak purity index is greater than single point threshold. so as to confirm peak identity.

Observation

Peak	Retention Time	Area	Peak purity index	Single point threshold
Acid	2.811	2388135	0.999994	0.999940
Basic	2.846	2171185	0.999989	0.999949
Heat	2.857	2097816	0.999993	0.999948
Light	2.839	2007782	0.999999	0.999946

Remarks

When exposed to heat and light conditions, the Trimetazidine Hydrochloride degrades. However none of the degradation products interfere with the Trimetazidine Hydrochloride peak as shown by the fact that the peak ins pure and positively matched with Trimetazidine Hydrochloride standard.

For acidic exposure, there appears to be no significant degradation. The peak eluting at the retention time corresponding to Trimetazidine Hydrochloride is pure and positively matched with that of the Trimetazidine Hydrochloride.

Trimetazidine Hydrochloride is completely degraded after exposure to Basic condition. There is no Trimetazidine Hydrochloride peak in this chromatogram.

Linearity

To check the Linearity prepare a dilution series of standard solution from 40 to 160% of the nominal concentration. Inject separately one times each concentration level & calculate correlation coefficient, r^2 from the calibration curve.

Trimetazidine Hydrochloride Stock solution: Dissolve 175.00 mg Trimetazidine Hydrochloride API into 200 ml volumetric flask with diluent. (0.875 mg/ml of Trimetazidine Hydrochloride).

Concentration level in (%) of the active ingredients concentration	Volume of stock solution added (ml) in 50 ml volumetric flask with mobile phase	Approx. final concentration in (mg/ml)
40	4	0.070
60	6	0.105
80	8	0.140
100	10	0.175
120	12	0.210
160	16	0.280

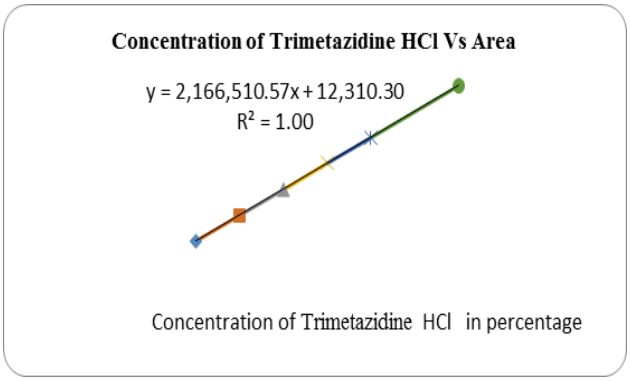
Acceptance Criteria

- Correlation coefficient: ≥ 0.995
- Intercept: To be reported
- Slope regression line: To be reported

Observation

Table: Different concentration of Trimetazidine Hydrochloride and Respective Peak Area.

Concentration level in (%) of the active ingredients concentration	Approx. final concentration in(mg/ml)	Peak area for Trimetazidine Hydrochloride	
	Trimetazidine Hydrochloride	Individual	Average
40	0.070	879088	879706
		880672	
		879359	
60	0.105	1310906	1311602
		1311652	
		1312247	
80	0.140	1742010	1741907
		1742196	
		1741514	
100	0.175	2183702	2183328
		2183551	
		2182732	
120	0.210	2612165	2611748
		2612230	
		2610847	
160	0.280	3477335	3478030
		3478385	
		3478369	



Graph 1: Different concentration of Trimetazidine Hydrochloride VS Average peak area.

From Graph-1: Regression equation , y = 2166510+ 12310 R^2 = 1.0

Correlation coefficient R^2	1.0
Intercept	2166510
Slope of regression line	12310

Acceptance Criteria & Results

Sl. No.	Acceptance Criteria	Results
01.	Correlation coefficient : ≥ 0.995	1.0
02.	Intercept : To be reported	2166510
03.	Slope regression line : To be reported	12310

Range

Data taken from linearity studies to establish range.

Remarks: Based on the test results of linearity, accuracy and precision the range of method is established as 80 – 120% of the target concentration.

Acceptance Criteria & Results

Acceptance Criteria	Results
80 – 120 % of the limit concentration of active ingredient.	Complies

Precision

System precision (additional test for system suitability)

To check the repeatability of the system, Inject the standard solution 6 times, immediate one after another, under conditions as similar as possible. Calculate the coefficient of Variation.

Acceptance Criteria

System is suitable if coefficient of variation is less then 2.0%.

Observation

Trimetazidine Hydrochloride

Table: Ten injection reading of standard solution.

No. of Sample	Peak area for Trimetazidine Hydrochloride	Average Area	Coefficient of variation (%)
01.	2190155	2190124	0.028
02.	2189680		
03.	2191087		
04.	2190412		
05.	2190139		
06.	2188948		
07	2190079		
08	2190358		
09	2189625		
10	2190756		

Acceptance Criteria & Results

Sl. No.	Acceptance Criteria	Results
01.	Coefficient of variation is less then 2.0%.	0.028%

Method precision (Repeatability)

To check the repeatability of the method, prepare separately the sample solution 6 times, immediately one after another, under conditions as similar as possible. Calculate the result for 6 determinations and calculate the coefficient of variation.

Observation

Trimetazidine Hydrochloride

Table: Six injection reading of standard & sample solutions.

Sl. No	Peak area for Trimetazidine Hydrochloride (Standard)	Average Area	Coefficient of variation (%)	Peak area of Trimetazidine Hydrochloride (Sample)	Content of Trimetazidine Hydrochloride in %	Coefficient of variation (%)
01.	2190155	2190070	0.033	2155494	96.80	0.70
02.	2189680			2155513	97.03	
03.	2191087			2153661	96.86	
04.	2190139			2144542	96.23	
05.	2188948			2158016	96.54	
06.	2190070			2189491	98.20	
Remarks: Coefficient of variation for 6 replicate for sample is 0.70 %						

Acceptance Criteria & Results

Sl. No.	Acceptance Criteria	Results
01.	The relative standard deviation for n ≥ 6, (6 determinations at 100 % concentration) should be ≤ 2.0 %	0.70%

Intermediate precision

The intermediate precision for the assay of Trimetazidine Tablet 35 mg should be determined by comparison of two independent repeatability experiments on 2 different days. The data of the 1st day can be taken from the analysis of 'Repeatability'. The second set of experiments (method precision for assay) is to be performed by a different analyst and different days.

Calculate the relative standard deviation from the results on each day.

Data for intermediate precision by two different analysts.

Product: Trimetazidine Tablet 35 mg						
Location: lab-2				lab-1		
Instrument used: Shimadzu HPLC with LC Solution Software (ID : HGER&D-015)				Alliance HPLC with Empower Software (ID : HGER&D -024)		
Date of analysis: 08.02.2014				03.03.2014		
Trimetazidine Hydrochloride				Trimetazidine Hydrochloride		
SL No.	**Average Area of Standard**	**Area of Samples**	**% Assay**	**Average Area of Standard**	**Area of Samples**	**% Assay**
1.	2190070	2155494	96.80	2532692	2471350	97.03
2.		2155513	97.03		2490201	97.80
3.		2153661	96.86		2496343	97.03
4.		2144542	96.23		2478133	96.71
5.		2158016	96.54		2488955	97.14
6.		2189491	98.20		2476593	97.17
Mean Assay, n = 6			96.94	Mean Assay, n = 6		97.14
Standard deviation, n = 6			0.68	Standard deviation, n = 6		0.36
Relative standard deviation, n = 6			0.69	Relative standard deviation, n = 6		0.37
Mean value of Assay different between two analyst , Δ						0.20%
Remarks : Mean value of Assay different between two analyst , i.e. Δ is 0.20%						

Acceptance Criteria & Results

Sl. No.	Acceptance Criteria	Results
01.	RSD for n≥ 6 is as per repeatability day 1 and mean values difference between day 1 and day 2 i.e. Δ < 2.0% absolute.	0.20%

Limit of detection (LOD) and Limit of quantification (LOQ)

Establish the limit of detection for Trimetazidine Hydrochloride based on the standard deviation of the response and the slope method.

$$\text{Limit of detection(LOD)} = \frac{3.3\times\sigma}{S}$$

$$\text{Limit of quantification (LOQ)} = \frac{10\times\sigma}{S}$$

Where

σ = The standard deviation of the response(STEYX)

S = The slope of the calibration curve

Observation

Trimetazidine Hydrochloride

Table: Six injection reading of standard solution.

No. of Sample	Concentration	Trimetazidine Hydrochloride Area
01.	40%	879706
02.	60%	1311602
03.	80%	1741907
04.	100%	2183328
05.	120%	2611748
06.	160%	3478030
Correlation Co-efficient		1.00
STEYX		2957.6
SLOPE		2166510
Limit of Detection		0.0045%
Limit of Quantification		0.0137%

Precession Limit of Quantification

No. of Sample	Name of Solution	Peak area for Trimetazidine Hydrochloride	Relative Standard Deviation
01.	LOQ 0.0137% Solution	26494	0.427
02.	LOQ 0.0137% Solution	26324	
03.	LOQ 0.0137% Solution	26520	
04.	LOQ 0.0137% Solution	26224	
05.	LOQ 0.0137% Solution	26414	
06.	LOQ 0.0137% Solution	26333	

Acceptance Criteria & Results

Sl. No.	Acceptance Criteria	Results
01.	The relative standard deviation for n ≥ 6, (6 determinations at LOQ concentration) should be ≤ 2.0 %	0.427

Accuracy or Recovery

The accuracy of the method is evaluated by samples spiked with active ingredients. Data from triplicate determinations should be collected at 3 concentration levels i.e. 80%, 100 % & 120% of the label claim of the active ingredient. The accuracy is expressed in recovery rates.

Trimetazidine Hydrochloride Stock solution: Dissolve 175.00 mg Trimetazidine Hydrochloride API into 200 ml volumetric flask with diluent. (0.875 mg/ml of Trimetazidine Hydrochloride).

Inject 6 replicates at each level.

Concentration level in (%) of the active ingredients concentration	Volume of stock solution added (ml) in 50 ml volumetric flask with mobile phase	Approx. final concentration in (mg/ml)
80	8	0.140
100	10	0.175
120	12	0.210

Preparation of Trimetazidine Tablet 35 mg accuracy test solutions

Take three 200 ml volumetric flask and labeled it as 80%, 100% & 120%.Weigh and transfer placebo equivalent to 5 tablets into the marked volumetric flask each. Weigh 140.0 mg, 175.0 mg and 208.80 mg of Valsartan API. And add it into the 80%, 100%, 120% marked volumetric flask respectively. Add 200 ml diluent each volumetric flask respectively, and performed as assay sample preparation. Transfer 10 ml of this each solution into 50 ml volumetric flask and volume upto the mark with the mobile phase Prepare at least 3 samples at each level.

Following table describe the concentration of sample at different level.

Concentration level in (%) of the active ingredients concentration	Approx. final concentration in (mg/ml)
	Trimetazidine Hydrochloride
80 x 3 sample	0.140
100 x 3 sample	0.175
120 x 3 sample	0.210

Observation

The sample solution for evaluating the Accuracy / Recovery was prepared as 80%– 120% of nominal analyte of Trimetazidine Hydrochloride.

Concentration of Trimetazidine Hydrochloride (mg/ml)	% of nominal concentration	Average Peak area (Standard)	Average Peak area (Sample)	Recovery from sample	% Recovered
0.140	80	1742163	1734927	0.0391419	99.56
0.175	100	2184435	2184091	0.174972	99.98
0.210	120	2612624	2631391	0.211508	100.72
				Average	100.09
				RSD	0.587%
				Max.	100.72%
				Min.	99.56%

Remarks: Individual recovery for Trimetazidine Hydrochloride is from (100.72–99.56)% and mean recovery is 100.09%.

Acceptance Criteria & Results

Sl.No.	Acceptance Criteria	Results
01.	Individual recovery % must be between 97 -103 %	100.72-99.56
02.	Mean recovery % must be between 98 -102 %	100.09%

Robustness

Stability of the analytical solutions

The stability of analytical solution is demonstrated by carrying out the analysis on the Reference and Test solution immediately after they are prepared and then at suitable intervals at room temperature.

The test solution to be kept on bench top under normal laboratory conditions and to be analyzed at suitable time intervals to establish bench top solution stability up to 8 hrs.

In a table summarize the % change between the initial results and the results at each time point calculated with respect to the fresh standard where appropriate.

Standard and sample solutions are prepared as per test method and analyzed initially and at different time intervals by keeping the solution at room temperature (about 25 °C).

Trimetazidine Hydrochloride

Standard Solution			Sample solution	
Time in Hours	**Area**	**Results**	**Area**	**Results**
Initial	2074406	-	2046927	-
4	2072127	98.50%	2051224	97.43%
8	2072928	98.92%	2048352	96.97%
Mean		98.71%		97.20%
Standard Solution Stability		0.42%	Sample Solution Stability	0.46%

Remarks: From the above study, there is no significant change in % result of standard & sample solution a suitable interval after 4 hours & 8 hours.

Sl. No.	Acceptance Criteria	Results (%)
01.	Standard solution: ± 2.0% with regard to initial	0.42%
02.	Sample solution: ± 2.0% with regard to initial	0.46%

Influence of the variation in test parameters

The influence of slightly changed parameters of the chromatographic conditions must be tested to demonstrate sufficient robustness of the method. In detail, effects of the change of flow rate, composition of mobile phase and different brand of analytical column and temperature should be studied. The tests are carried out by using standard solution spiked and varying each of the parameters of chromatography mentioned above as follows:

Flow rate	:	0.9 and 1.1 ml /min (required 1.0 ml/min)
Amount of Methanol for mobile phase	:	392 ml and 408 ml (required 400 ml)
Analytical column	:	Column with same specifications of different brands or different lots of same manufacturer is considered as an additional part of robustness test and is recommended to verified or validated during routine work.
Temperature	:	25°C & 35°C (required temperature 30°C)
Detection wavelength	:	As per the current guidelines published in BP and Ph. Eur. change in detection wavelength is not allowed.

Acceptance Criteria: In each experiments

Tailing factor should be consistent with initial

Show the chromatograms of each run with individually changed parameters.

A summary of the various conditions tested should be added.

If the results obtained for the proposed parameters are not meeting acceptance criteria, then the influence to be demonstrated at the intermediate level of the above proposed parameters.

Observation

Change in flow rate

Mobile Phase	Flow Rate ml/min	Ret.Time	Area	Theoretical plates
		Trimetazidine Hydrochloride	Trimetazidine Hydrochloride	Trimetazidine Hydrochloride
Methanol for mobile phase 400.0 ml	0.9 ml	3.157	2306741	2875.87
Methanol for mobile phase 400.0 ml	1.0 ml	2.858	2073464	2767.05
Methanol for mobile phase 400.0 ml	1.1 ml	2.606	1887710	2647.28

Change amount of Methanol for mobile phase

Mobile Phase	Flow Rate ml/min	Ret.Time	Area	Theoretical plates
		Trimetazidine Hydrochloride	Trimetazidine Hydrochloride	Trimetazidine Hydrochloride
Methanol for mobile phase 392.0 ml	1.0 ml	2.854	2076218	2752.26
Methanol for mobile phase 400.0 ml	1.0 ml	2.858	2073464	2767.05
Methanol for mobile phase 408.0 ml	1.0 ml	2.857	2074062	2772.08

Change in Temperature

Mobile Phase	Temperature	Ret.Time	Area	Theoretical plates
		Trimetazidine Hydrochloride	Trimetazidine Hydrochloride	Trimetazidine Hydrochloride
Methanol for mobile phase 400.0 ml	25^0C	2.857	2075359	2771.3
Methanol for mobile phase 400.0 ml	30^0C	2.858	2073464	2767.05
Methanol for mobile phase 400.0 ml	35^0C	2.847	2071074	2795.80

Change analytical Column

Mobile Phase	Flow Rate ml/min	Different Brands Column	Ret.Time	Theoretical plates
			Trimetazidine Hydrochloride	Trimetazidine Hydrochloride
Methanol for mobile phase 400.0 ml	1.0 ml	Waters C18, 5µ, 4.6 X250mm	2.858	2767.05
Methanol for mobile phase 400.0 ml	1.0 ml	Water, Xterra Columns, 5µ,C18, 4.6 X250mm	3.007	3336.09

Remarks: From the above data it is clear that change in flow rate, methanol in mobile phase, Temperature & different brand of column have no significant effect on retention time & Theoretical plates.

Acceptance Criteria & Result

Acceptance Criteria	Result
Retention time &Theoretical plates should be consistent with initial	Consistent

Filter suitability test

Inject the following solutions into the chromatographic system.

- Test solution spiked with active ingredient at label claim concentration.
- Above solution filtered with different makes of the filters.

Calculate the % content in the above solutions.

Compare the observed results in a table and give a statement for the suitability of the filters.

0.45µ.disc filter			0.20µ.disc filter	
Content /Tablet(mg)		Assay in %	Content/ Tablet(mg)	Assay in %
Trimetazidine Hydrochloride	33.90 mg	96.86	33.90 mg	96.86

Remarks: From the above study, there is no significant change % content in the above solutions by changing disc filter 0.45µ. & 0.20µ.

Acceptance Criteria & Result

Specification	Result
Will not be observed significant change in % content	Complies

Analysis by different machine (HPLC)

Analysis on the Reference solution is to be performed by different HPLC system to demonstrate sufficient robustness of the method.

Shimadzu HPLC System with PDA Detector (ID-HGER&D-015)	Waters HPLC System with UV Detector (ID-HGER&D-024)
Release in %	Release in %
96.94%	97.14%

Remarks: Difference of two instrument results are 0.20 %.

CONCLUSION

A simple, sensitive, specific, accurate and precise stability indicating HPLC method was validated for the routine analysis of tablet dosage form of trimetazidine. The method is sensitive enough for the detection of analyte in pharmaceutical formulation when compared to the research works found in the literature. The results of forced degradation studies reveal that the method is stability indicating. The proposed method has the capability to separate the analyte from their degradation products obtained during forced degradation studies and excipients found in tablets. The method can be employed for the routine analysis of trimetazidine.

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