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Stability-indicating Rp-HPLC method for the estimation of Metoprolol Succinate and Hydrochlorothiazide in tablet dosage form

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Abstract

An easy, specific, accurate and precise RP-HPLC method was developed and validated for the concurrent estimation of metoprolol succinate and hydrochlorothiazide in pharmaceutical formulation with forced degradation studies. The method was developed by means of Enable C 18G column (250 ×4.6 mm, 5 µm) with mobile phase consisting of acetonitrile and 0.05 % trifluoroacetic acid in water (70:30 %v/v) with a flow rate of 0.7 mL/min. UV detection was carried out at 222 nm. The retention time for metoprolol succinate and hydrochlorothiazide were found to be 4.012 and 4.698 min respectively. The proposed method was validated for linearity, range, accuracy, precision, robustness, LOD and LOQ. Linearity was observed over a concentration range 2-40 µg/ml for metoprolol succinate (r2 =0.9999) and 0.5-80 µg/ml for hydrochlorothiazide (r2 =0.9990). The % RSD for intraday and nterday precision was found to be 0.57 and 0.68 for metoprolol succinate and 0.52 and 0.41 for hydrochlorothiazide. The LOD and LOQ were found to be 0.05 µg/ml and 0.16 µg/ml for metoprolol succinate and LOD and LOQ were found to be 0.04 and 0.15 µg/ml for hydrochlorothiazide respectively. Metoprolol succinate and hydrochlorothiazide were subjected to stress conditions of degradation including acidic, alkaline, oxidative, thermal and photolysis.

Keywords: Metoprolol Succinate, Hydrochlorothiazide, RP-HPLC and Forced Degradation.

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1. Introduction

Metoprolol Succinate(MET), sterically elected as (±) 1- (isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) [Figure 1]. This is a cardio discerning drug second-hand single-handedly or blend with other medicines to indulgence hypertension and a multiplicity of cardiovascular disorder. The accomplishment of Metoprolol succinate is mediate from end to end the β1-selective adrenoceptor obstruction, thus causing reduction in heart rate and cardiac output. Prose inspection disclose a blend of analytical technique are reported either individually or in combination with other drugs include spectrophotometric, HPLC in pure form, pharmaceutical dosage forms and natural fluids.

Hydrochlorothiazide(HCTZ)[Figure 2] chemically as 6-chloro-3,4-dihydro-2H- 1,2,4-benzothiadiazine-7-sulphonamide1,1-dioxide is a thiazide preparation second-line for the achievement of hypertension, congestive heart breakdown, hepatic cirrhosis and some nephron diseases. This is a diuretic, which inhibits the ability of the kidney to keep hold of water by growing the elimination of Na, chloride and, to a lesser extra room, potassium ions. Literature survey reveals various analytical methods have been reported for the estimation of hydrochlorothiazide either alone or in combination with other drugs in pure form, pharmaceutical dosage forms and in biological samples by means of scatter reflectance spectroscopy, HPLC, electrophoretic and electrochemical models. The blend dose of metoprolol Succinate and hydrochlorothiazide is competent in the activities of mild to realistic hypertention. The combination therapy was not only further efficient than monotherapy with the temperament mechanism but the combination product allows a low-dose multi-drug practice as an option to high-dose monotherapy, in that way, minimizing the probability of dose-related side-effects . A variety of analytical methods were reported for concurrent estimation of metoprolol succinate and hydrochlorothiazide in pure drug , pharmaceutical formulations and biological fluids by spectrophotometric (Chitlange et al 2012., Gupta et al 2008) , HPLC(Singh et al 2009.,Garg and Saraf 2008 ., Rawool and Venkatchlam 2011 ., Tsvetkova and Peikova 2013) and Electrophoretic (Alnajjar et

al 2013). Stability indicating RP-HPLC methods(Kumar and Sankar 2016., Kumar and Sankar 2016., Kumar and Sankar 2016., Kumar and Asha 2019.,Kumar et al 2019., Kumar et al 2019., Kumar et al 2019) have significant role to determine the intrinsic stability of drug molecules and find degradation pathays. Only one stability indicating RP-HPLC method(Shinde et al 2014) was reported for the simultaneous estimation of both drugs in pharmaceutical formulation, but the developed method has long retention time and complex mobile phase composition. Therefore, in the present study an attempt was made to develop a simple, precise, accurate RP-HPLC method with forced degradation studies for the analysis of metoprolol succinate and hydrochlorothiazide in pharmaceutical formulation.

2. MATERIALS AND METHOD:

Materials and Chemicals

Metoprolol Succinate and hydrochlorothiazide standard were obtained as gifted sample from pharma industry. Metoprolol succinate and hydrochlorothiazide tablets (DUTOPROL TABLETS) containing hydrochlorothiazide 12.5 mg and metoprolol succinate 23.75 mg were purchased from local pharmacy. HPLC grade water and acetonitrile was from MERCK India Ltd. HPLC grade methanol was from standard reagent pvt Ltd Hyderabad. Analytical grade hydrochloric acid, sodium hydroxide, hydrogen peroxide and trifluroacetic acid was from SD Fine chemicals Mumbai, India. Nylon membrane filters 0.2 µm and 0.45 µm were from PALL life sciences Mumbai, India. Ultrasonicator used was from LAB india Ltd Mumbai. pH meter was of Elico LI 120 make. UV Specctrophotometer was of Elico SL 210 model consisted of spectral treats software.

Instrumentation

The chromatographic system used for the method development and validation consisted of Shimadzu HPLC comprising of LC-20AD binary gradient pump, a variable wavelength programmable SPD-20A detector and an SCL 20A system controller. A Rheodyne injector 7725i fitted with a 20 µL loop was used and data were recorded and evaluated by use of LC solutions software version 5.0.

Chromatographic conditions

Chromatographic analysis was performed on Enable C18 G column (250 x 4.6 mm i.d, 5µ) .The mobile phase consisted of acetonitrile and 0.05 % trifluoroacetic acid in water (70:30 % v/v). The flow rate was 0.7 mL/min, injection volume was 20 µL and detection was carried out at 222 nm using a UV detector.

Preparations of metoprolol succinate and hydrochlorothiazide stock solution

Stock solution of metoprolol succinate (1000 µg/ml) and hydrochlorothiazide(1000 µg/ml) was prepared separately by transferring accurately weighed 50 mg of metoprolol succinate and 50 mg of hydrochlorothiazide into a 50 ml volumetric flask and to it added a 20 ml methanol. The mixture was sonicated for 5 min to dissolve the drug and the solution was diluted up to the mark with methanol. Standard solutions of metoprolol succinate (100 µg/ml) and hydrochlorothiazide (100 µg/ml) were prepared by diluting 10 ml of standard stock solution to 100 ml in a volumetric flask with the mobile phase. To prepare a binary mixture of hydrochlorothiazide and metoprolol succinate appropriate volume of standard solution was transferred into a 10 ml volumetric flask and diluted with mobile phase to get a solution containing 12.5 µg/ml of hydrochlorothiazide and 23.75 µg/ml of metoprolol succinate.

Analysis of metoprolol succinate and hydrochlorothiazide in combined dosage form

Accurately weighed about twenty tablets and average weight of tablet was determined. The tablets were transferred into mortar and triturated to a fine powder form. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol succinate was transferred into a 100 ml volumetric flask .To it 20 ml HPLC grade methanol was added and sonicated for 5 min to dissolve the drugs. The content of the flask was kept for 10 min at laboratory temperature and diluted up to mark with HPLC grade methanol this gives a concentration of hydrochlorothiazide 125 µg/ml and metoprolol Succinate 237.5 µg/ml. The above solution was filtered through 0.2 µ membrane filter. The 1 ml of the filtrate was transferred into a 10 ml volumetric flask and diluted with mobile phase to get a concentration of 12.5 µg/ml and 23.75 µg/ml for hydrochlorothiazide and metoprolol succinate respectively.

Method validation

The method was validated for accuracy, precision, linearity, specificity, robustness, limit of detection, limit of quantitation.

Linearity

Linearity was performed by preparing standard solutions of hydrochlorothiazide and metoprolol Succinate at different concentration levels. Hydrochlorothiazide was prepared in the concentration range of 0.5-80 µg/mL and 2-40 µg/mL for metoprolol succinate. Twenty micro litres of each concentration from both drug solutions was injected in duplicate into the HPLC system. The response was carried out at 222 nm and the corresponding chromatograms were recorded from these mean peak areas were calculated. The calibration curve was plotted by taking concentration on x-axis and peak areas on y-axis for both the drugs.

Accuracy

The accuracy of the method evaluated by standard addition method in which a known amount of standard drug was added to the fixed amount

of pre-analyzed tablet solution. Percent recovery of hydrochlorothiazide and metoprolol Succinate was calculated at three concentration levels of 80 %, 100 % and 120 %. The solutions were analyzed in triplicate at each level. The percent recovery and % RSD at each level was calculated.

Precision

Precision of the method was evaluated as system precision and method precision.

To study the system precision, six replicate standard solutions of hydrochlorothiazide and metoprolol succinate were analysed. The percent relative standard deviation (% RSD) was calculated for both hydrochlorothiazide and metoprolol Succinate.

Method precision of the analytical method was carried out on six preparations from the tablet formulation and percentage amount of hydrochlorothiazide and metoprolol Succinate in the tablet formulation was calculated. The intraday and interday precision study were conducted for both hydrochlorothiazide and metoprolol succinate. The mean % assay value, standard deviation and percent relative standard deviation was calculated.

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

LOD was measured by serially diluting the standard solutions of hydrochlorothiazide and metoprolol succinate and determining the concentration was response of sample peaks are three times the noise peak. LOQ was measured by serially diluting the standard solutions of hydrochlorothiazide and metoprolol succinate and determining the concentration was response of sample peaks are ten times the noise peak.

Robustness

Robustness of the method was determined by making slight changes in composition of organic phase ± 5 %, flow rate by ± 0.1 ml/min and detection wavelength by ± 2 nm.

Specificity

The specificity of the proposed method was determined against blank and placebo applications. Here mobile phase was used as blank and excipients like starch,lactose, magnesium stearate were used as placebo.

Forced Degradation studies

Different stress conditions were used for the forced degradation studies of formulation .These was also used to evaluate the specificity of the method. All the samples were diluted with mobile phase and filtered through 0.2 µ membrane filter.

Acidic conditions

Weighed accurately about twenty tablets and triturated it to a fine powder form. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol succinate was transferred into a 100 ml volumetric flask. To this added a 50 ml of diluent and sonicated for 10 min to dissolve the drug completely. Then 10 ml of 5N HCl was added to it, refluxed for 6 hr at 60 0C, cooled to room temperature, neutralized with 5N NaOH and diluted up to the mark with the diluent.

Alkaline conditions

Weighed accurately about twenty tablets and triturated it to a fine powder form. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol succinate was transferred into a 100 ml volumetric flask. To this added a 50 ml of diluent and sonicated for 10 min to dissolve the drug completely. Then 10 ml of 5N NaOH was added to it, refluxed for 6 hr at 600C , cooled to room temperature, neutralized with 5N HCl and diluted up to the mark with the diluent. The above sample solution was filtered through 0.2 µ nylon membrane filter. Pipetted 1 ml of the above filtered sample solution into a 10 ml volumetric flask and volume made up to the mark with diluent.

Oxidative degradation

Weighed accurately about twenty tablets and triturated it to a fine powder form. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol Succinate was transferred into a 100 ml volumetric flask. To this added a 50 ml of diluent and sonicated for 10 min to dissolve the drug completely. Then 5 ml of 30 % hydrogen peroxide was added, refluxed for 2 hr at 60 0C , then cooled to room temperature and diluted up to the mark with diluents. The above sample solution was filtered through 0.2 µ nylon membrane filter. Pipetted 1 ml of the above filtered sample solution into a 10 ml volumetric flask and volume made up to the mark with diluent.

Thermal degradation

Weighed accurately about twenty tablets and triturated it to a fine powder form. The powder sample was subjected to thermal stress at 105 0C for about 2 days. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol succinate was transferred into a 100 ml volumetric flask. . To this added a 50 ml of diluent and sonicated for 10 min to dissolve the drug completely the diluted up to mark with diluents. The above sample solution was filtered through 0.2 µ nylon membrane filter. Pipetted 1 ml of the above filtered sample solution into a 10 ml volumetric flask and volume made up to the mark with diluent.

Photolytic Degradation

Weighed accurately about twenty tablets and triturated it to a fine powder form. The powder sample

was subjected to UV light in a photostability chamber for about 10 days. An aliquate of the powder equivalent to 12.5 mg of hydrochlorothiazide and 23.75 mg of metoprolol Succinate was transferred into a 100 ml volumetric flask. To this added a 50 ml of diluent and sonicated for 10 min to dissolve the drug completely the diluted up to mark with diluents. The above sample solution was filtered through 0.2 µ nylon membrane filter. Pipetted 1 ml of the above filtered sample solution into a 10 ml volumetric flask and volume made up to the mark with diluent.

3. RESULTS AND DISCUSSION:

Optimization of chromatographic conditions

In the present work an analytical method based on RP-HPLC using UV detector was developed and validated for simultaneous estimation of hydrochlorothiazide and metoprolol succinate in pharmaceutical formulation. The selection of analytical conditions was based on the chemical nature of hydrochlorothiazide and metoprolol Succinate. A systematic study of various factors were undertaken by varying one parameter at a time and keeping all other conditions constant for development of analytical method. Both hydrochlorothiazide and metoprolol Succinate were soluble in polar solvents therefore RP-HPLC was chosen. The selection of stationary phase has been done on the basis of back pressure, resolution, peak shape, theoretical plates and day to day reproducibility in retention time resolution between hydrochlorothiazide and metoprolol succinate peaks. After evaluating all these factors Enable C18 G column (250 x 4.6 mm i.d, 5µ) was chosen for the analysis. For optimization of mobile phase preliminary trials were conducted under isocratic conditions using mobile phases composed of mixture of solvents like water, methanol and actonitrile in different combinations. A mixture of acetonitrile and 0.05% trifluoroacetic acid in water at a ratio of 70:30 v/v was found to be most suitable of all the combinations since the chromatographic peaks obtained were have good system suitability parameters. The Flow rate of mobile phase was optimized based on resolution between chromatographic peaks and minimal solvent consumption. The flow rate of mobile phase was changed from 0.5-2 ml/min. It was found from trials that 0.7 ml/min flow rate was ideal for successful elution of both drugs. For selection of analytical wavelength standard solutions of both drugs were scanned in wavelength range of 200-350 nm. A detection wavelength of 222 nm was selected. The chromatogram of standard was shown in Figure 3.

Method validation

Linearity

Linearity was studied by preparing standard solutions at different concentration levels. The linearity ranges for metoprolol succinate and hydrochlorothiazide were found to be 2-40 µg/mL and 0.5-80 µg/mL respectively. The linear regression equation for metoprolol succinate was found to be 34059x + 1601 with correlation coefficient 0.9999. The linear regression equation for hydrochlorothiazide was found to be 24150x+11350 with correlation coefficient 0.9990. The calibration table for metoprolol Succinate and hydrochlorothiazide was shown in Table 1 and Table 2 respectively. The calibration curve of metoprolol Succinate and hydrochlorothiazide were shown in Figure 4 and Figure 5 respectively.

Accuracy

The percent recovery of hydrochlorothiazide and metoprolol succinate was found to be 100.42-100.56 % and 99.84-100.58%. This indicates the accuracy of the method. The results are shown in Table 3 & 4.

Precision

System precision

The %RSD for hydrochlorothiazide was found to be 1.31 and for metoprolol Succinate was found to be 0.66 which are within the acceptance criteria of not more than 2.0 indicates the precision of the method. Table 5.

Method Precision

The % RSD for Intraday and Interday precision assay results of six preparations for hydrochlorothiazide were found to be 0.52 and 0.41 respectively which are within the acceptance criteria of not more than 2.0 indicates the precision of method. The % RSD for Intraday and Interday precision assay results of six preparations for metoprolol Succinate were found to be 0.57 and 0.68 respectively which are within the acceptance criteria of not more than 2.0 indicates the precision of the method. Table 6.

Limit of detection and Limit of quantitation

The LOD and LOQ were found to be 0.05 µg/mL and 0.16 µg/mL for metoprolol succinate and the LOD and LOQ for hydrochlorothiazide were 0.04 µg/mL and 0.15 µg/mL respectively.

Robustness

To evaluate the robustness of the developed method, small deliberate variations in optimized method parameters were made. The effect of change in flow rate, change in pH , change in composition of mobile phase and detection wavelength on retention time, tailing factor and theoretical plates were studied. The method was found to be unaffected by small changes in flow rate, change in pH, change in composition of mobile phase and detection wavelength as shown in Table 7 and Table 8.

Specificity

Specificity is the ability to unequivocally assess the analyte in the presence of components that may be expected to be present. Typically, these might

include impurities, degradants or matrix. Specificity of an analytical method is its ability to accurately and specifically measure the analyte of interest without interference from blank or placebo. The peak purities of metoprolol succinate and hydrochlorothiazide were assessed by comparing the retention times of standard metoprolol succinate and hydrochlorothiazide and the sample, and good correlation was obtained between the retention time of the standard and sample. Placebo and blank were injected and there were no peaks. There is no interference of degradation peaks on drug peaks hence, the method is specific.

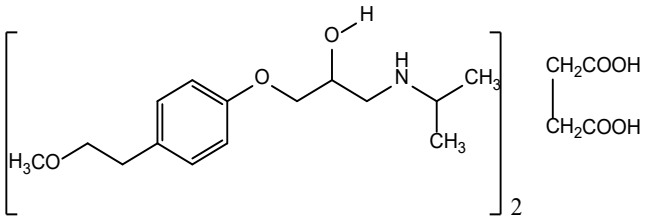

Figure 1. Structure of Metoprolol Succinate

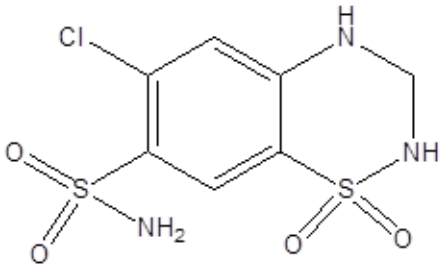

Figure 2. Structure of Hydrochlorothiazide

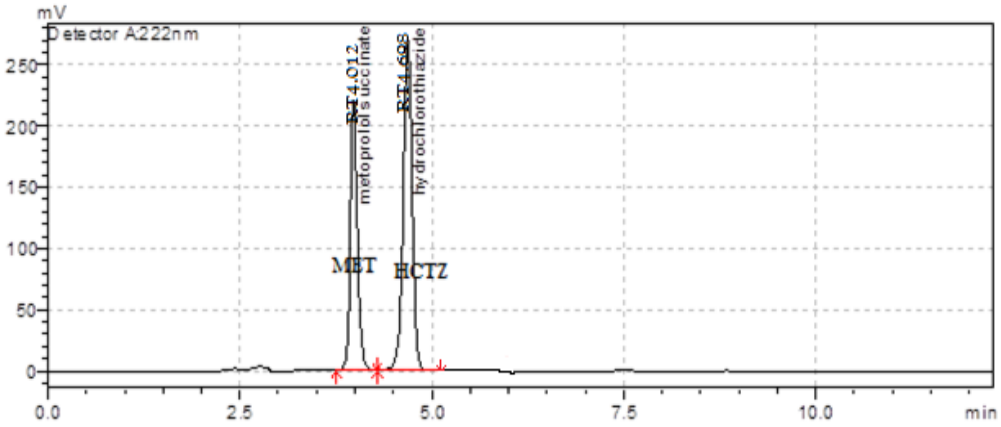

Figure 3. Chromatogram of Metoprolol Succinate and Hydrochlorothiazide

Table 1. Linearity data for Metoprolol succinate.

Level	Concentration of Metoprolol Succinate(µg/mL)	Mean peak area
Level-1	2	65474
Level-2	10	342160
Level-3	20	672341
Level-4	30	1029104
Level-5	40	1356946
	Slope	34059
	Intercept	-1601
	Correlation	0.9999
Coefficient		

Table 2. Linearity data for Hydrochlorothiazide

Level	Concentration of Hydrochlorothiazide (µg/mL)	Mean peak area
Level-1	0.5	13544
Level-2	10	246451
Level-3	20	496437
Level-4	30	728965
Level-5	40	985404
Level-6	50	1237331
Level-7	60	1478772
Level-8	70	1722531
Level-9	80	1898763
	Slope	24150
	Intercept	11350
Coefficient	Correlation	0.9990

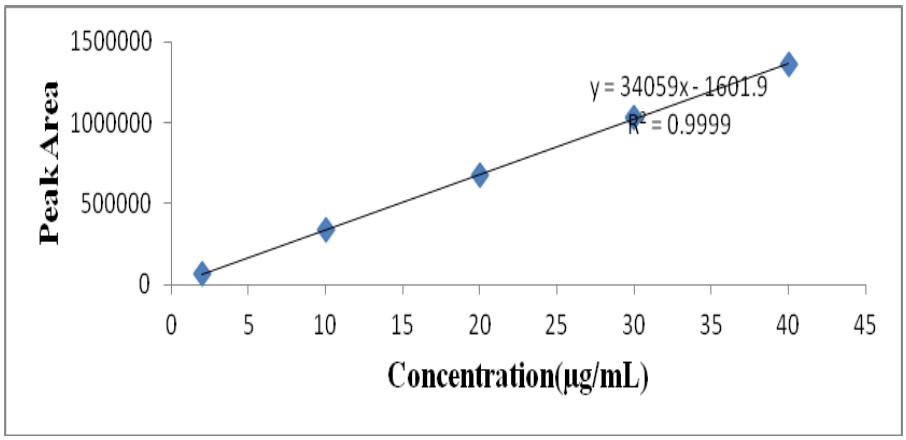

Figure 4. Linearity plot of Metoprolol Succinate

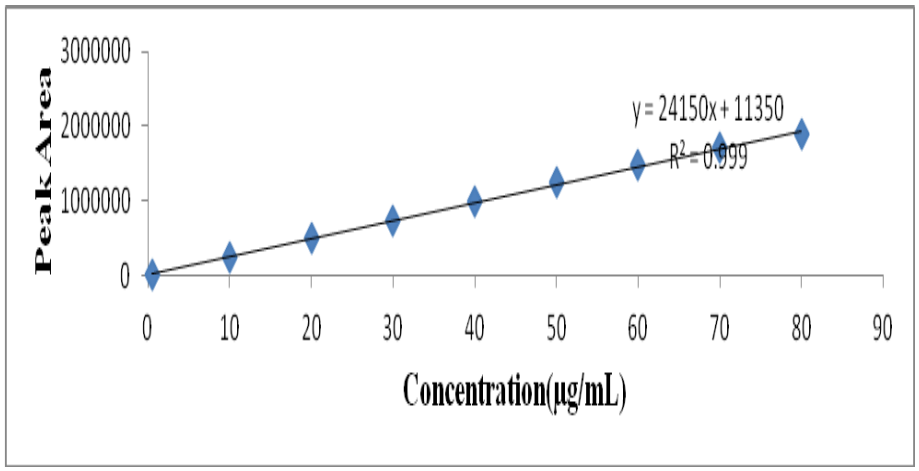

Figure 5. Linearity plot of Hydrochlorothiazide

Table 3. Accuracy results of hydrochlorothiazide

Accuracy level (%)	Amount taken(µg/mL)	Amount found(µg/mL)	% Recovery	Mean Recovery	% RSD
	16	15.94	99.62	100.42	0.83
80	16	16.22	101.31		
	16	16.08	100.52		
	20	20.12	100.63	100.56	0.14
100	20	20.14	100.73		
	20	20.09	100.41		
	24	24.16	100.60	100.42	0.11
120	24	24.11	100.46		
	24	24.06	100.21		

Table 4. Accuracy results of metoprolol succinate

Accuracy level (%)	Amount taken(µg/mL)	Amount found(µg/mL)	% Recovery	Mean Recovery	% RSD
	20	20.15	100.71	100.58	0.40
80	20	20.03	100.12		
	20	20.18	100.91		
	25	24.89	99.56	99.84	0.43
100	25	24.91	99.64		
	25	25.08	100.32		
	30	30.04	100.13	100.29	0.13
120	30	30.12	100.40		
	30	30.11	100.36		

Table 5. System precision results for hydrochlorothiazide and metoprolol succinate

Injection No.	Peak Area of Hydrochlorothiazide	Peak Area of Metoprolol Succinate
1	308066	812630
2	298460	819847
3	299262	827743
4	301884	814927
5	304528	822838
6	306974	819263
Mean	303195	819541
SD	3984	5428
%RSD	1.31	0.66

Table 6. Method precision results for hydrochlorothiazide and metoprolol succinate.

Set	Hydrochlorothiazide(%Assay)		Metoprolol Succinate(%Assay)	
	Intraday(n=6)	Interday(n=6)	Intraday(n=6)	Interday(n=6)
1	**100.15**	**100.46**	**99.98**	**100.74**
2	**100.47**	**100.40**	**100.69**	**100.16**
3	**100.84**	**100.29**	**100.09**	**99.13**
4	**99.66**	**100.12**	**99.34**	**99.52**
5	**99.96**	**99.69**	**100.72**	**100.84**
6	**99.41**	**100.96**	**100.82**	**100.38**
Mean	**100.08**	**100.32**	**100.27**	**100.12**
SD	**0.52**	**0.41**	**0.57**	**0.68**
%RSD	**0.52**	**0.41**	**0.57**	**0.68**

Table 7. Robustness results for metoprolol succinate

Conditions	% Assay	System Suitability parameters	
		Theoretical Plates	Tailing Factor
Flow Rate 0.9 mL/min	100.34	7466	1.11
Flow Rate 1.1 mL/min	100.31	7452	1.15
Mobile Phase- Water(25):Methanol(65)	100.25	7463	1.15
Mobile Phase- Water(15):Methanol(85)	100.23	7461	1.14
Mobile Phase pH 3.7	100.21	7452	1.14
Mobile Phase pH 3.3	100.32	7445	1.13
Wavelength 242 nm	100.24	7462	1.14
Wavelength 238 nm	100.36	7397	1.15

Table 8. Robustness results for hydrochlorothiazide

Conditions	% Assay	System Suitability parameters	
		Theoretical Plates	Tailing Factor
Flow Rate 0.9 mL/min	100.12	6525	1.16
Flow Rate 1.1 mL/min	100.25	6514	1.22
Mobile Phase- Water(25):Methanol(75)	100.28	6531	1.21
Mobile Phase- Water(15):Methanol(85)	100.22	6544	1.21
Mobile Phase pH 3.7	100.17	6553	1.22
Mobile Phase pH 3.3	100.14	6545	1.21
Wavelength 242 nm	100.08	6512	1.21
Wavelength 238 nm	100.19	6535	1.21

Table 9. Analysis of metoprolol succinate and hydrochlorothiazide in commercial formulation

Formulation	Labelled claim(mg)		Amount found*(mg)		%Recovery*±%RSD	
	MET	HCTZ	MET	HCTZ	MET	HCTZ
DUTOPROL TABLETS	12.5	23.75	12.51	23.79	100.08 ± 0.18	100.25 ±0.45

***Average of three determinations**

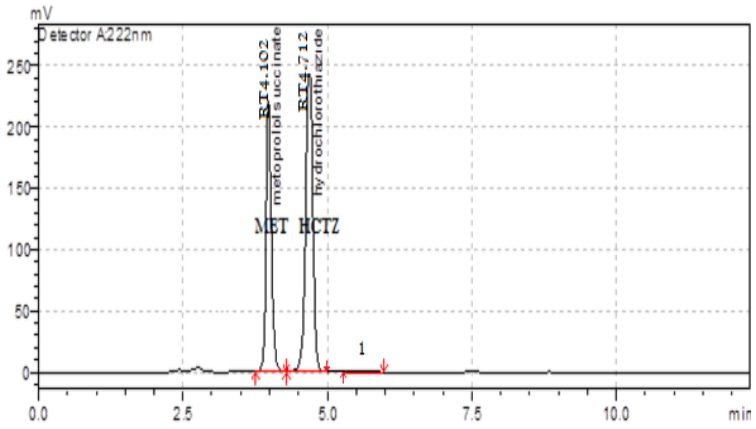

Figure 6. Acid degradation chromatogram

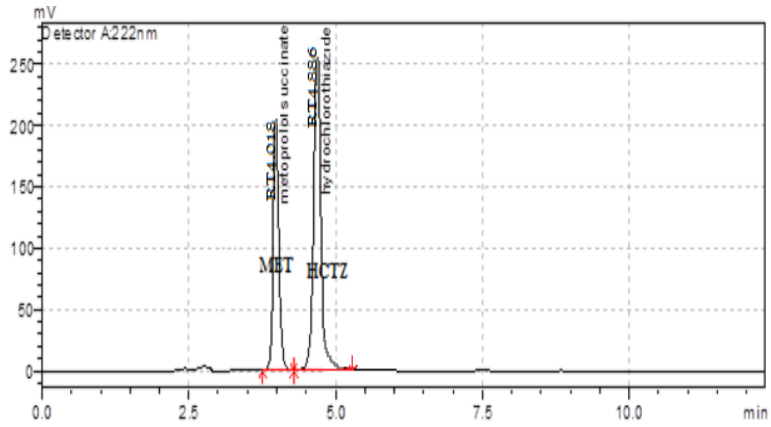

Figure 7. Base degradation chromatogram

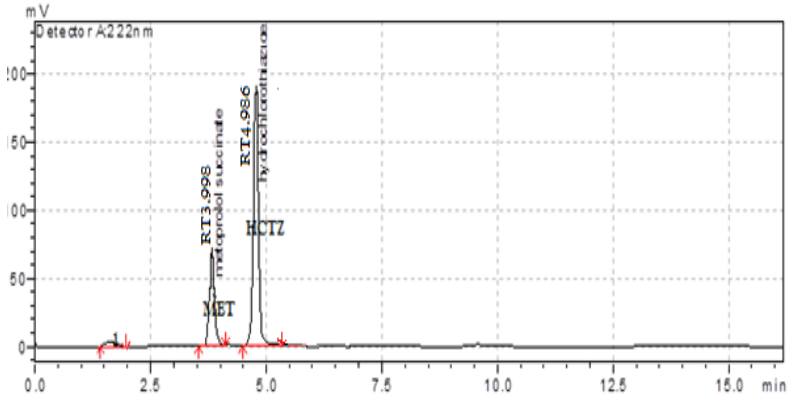

Figure 8. Oxidative degradation chromatogram

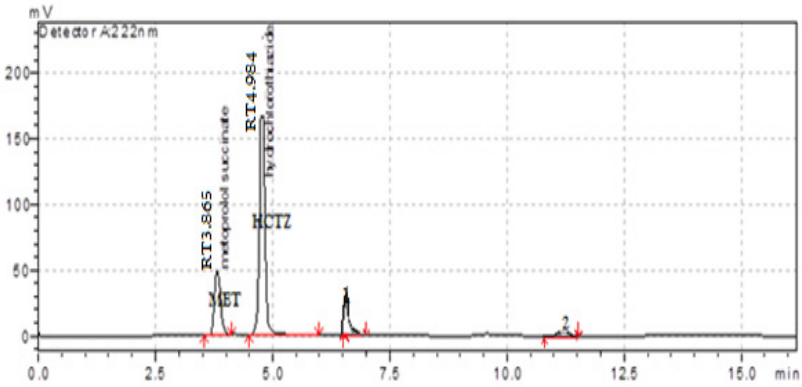

Figure 9. Thermal degradation chromatogram

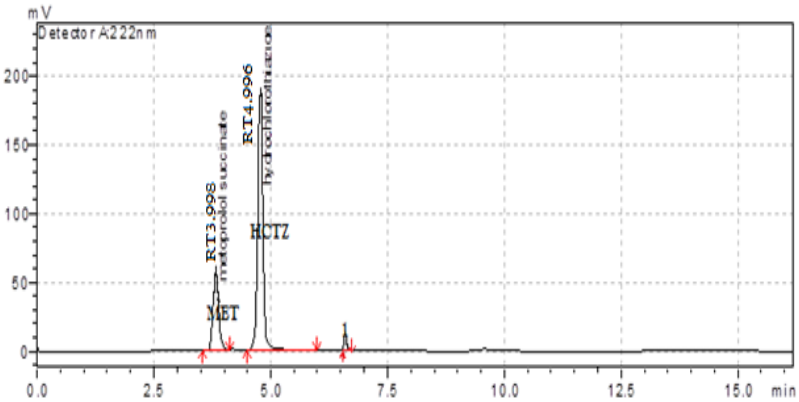

Figure 10. Photolytic degradation chromatogram

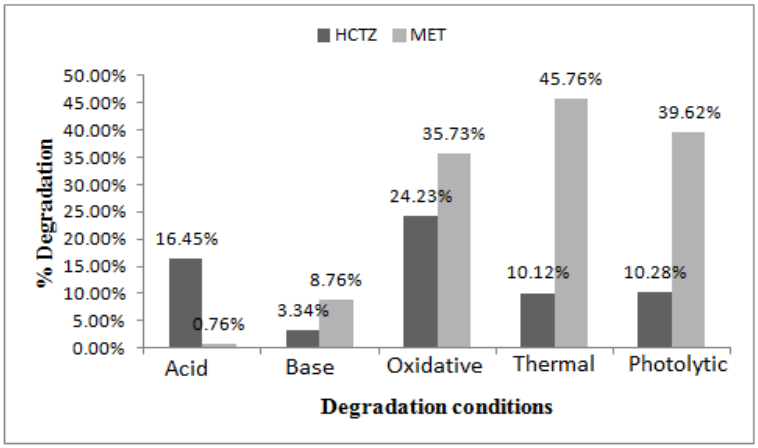

Figure 11. Presentation of degradation of HCTZ and MET in various conditions

CONCLUSION:

The proposed method for the simultaneous estimation of metoprolol succinate and hydrochlorothiazide validated as per the ICH guidelines and it is simple, specific and reliable. The data generated from the forced degradation studies enabled the evaluation of metoprolol Succinate and hydrochlorothiazide stability under a variety of ICH recommended conditions. These data are valuable for the safety and potency assessment of a drug product. Furthermore, this simple and rapid RP-HPLC method can also be used successfully for the determination of metoprolol succinate and hydrochlorothiazide in pharmaceutical formulations without any interference from the excipient.

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