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R E S E A R C H A R T I C L E

Development of Stability Indicating Assay Method for Antiemetic Drugs in Combined Dosage Formulation

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A B S T R A C T

A new stability indicating reversed-phase high performance liquid chromatography method was developed for assay of Domperidone and Pantoprazolein tablet. The separation was achieved on column (4.6 × 250mm, 5µm) using methanol and water (60:40, v/v) as mobile phase for assay and flow rate 0.7ml/min. Detection was carried out in U.V detector at 285.0 nm. The retention time of 4.36min approximately for Domperidone and Pantoprazole. The system suitability test shows the response with retention time, theoretical plate, tailing factor and peak area for both the drugs. The force degradation study was carried out by acid, alkali, peroxide and neutral at RT and the % degradation was 5.45% by acid5.50% by base6.24% by peroxide. The validation of method carried out using ICH guidelines. The developed method was accurate, precise, economic, fast, and selective for simultaneous determination of Domperidone and Pantoprazolein combined tablet formulation. The method gave good resolution for drugs.

Keywords: Domperidone, Pantoprazole, reversed phase high performance liquid chromatography, Stability-indicating method.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Analysis is important in every product but it is vital in medicines as it involves life. The assurance of quality is achieved through analysis of drug product. Stability testing is an important part of qualitative analysis. The purpose of stability testing isto evaluate shelf life period under variety of environmental factors such as temperature, humidity and light. The two main aspects of a drug product that play an important role in shelf life determination are assay of the active drug and degradation products generated during the stability study. Stability indicating method specially stress testing as recommended by the international conference on harmonization (ICH) guidelines and US FDA guidelines. The knowledge gained from stress testing can be useful for

(1) The development of stable formulation and appropriate packaging design

(2) Controlling of manufacturing and processing parameters

(3) Identification and isolation of toxic degradants during API synthesis

(4)Recommendation of appropriate storage conditions and shelf-life determination and

(5) Designing and interpreting environmental studies, as the degradation of the drug in the environment will often be similar to degradation observed during stresstesting studies.

Fixed dose combination containing Domperidone (DOM)andPantoprazole (PTZ) is a combination of an antiemetic drugs. Few Spectrophotometric and chromatographic methods have been reported for estimation of DOM in bulk pharmaceutical formulations. Several Spectrophotometric, chromatographic methods are also reported for determination of PTZ alone and in combination with other drugs from pharmaceutical formulations and biological fluids. But there is so far no stability indicating HPLC method is reported for assay in tablet dosage form. The following methods have developed for determination of DOM&PTZ in combined dosage form.

Domperidone is chemically 5-chloro-1-(1-[3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl) propyl]piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one. It is white to creamy-white, tasteless and odorless. Used as Anti-Emetics having mode of action as it is peripheral dopamine (D2) and (D3) receptor antagonist and blocks receptors at the chemo-receptor trigger zone.

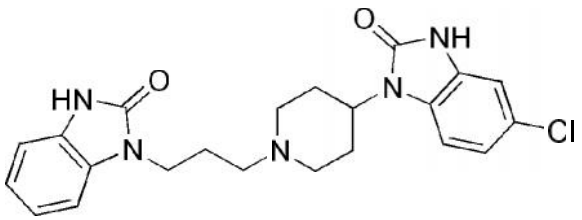

Fig 1: Structure of Domperidone

Pantoprazole is chemically (RS)-6-(Difluoro methoxy)-2-[(3,4-dimethoxypyridin-2-yl)methyl sulfinyl]-1H-benzo[d] imidazole. It is White to off-white, crystalline and practically odorless powder. Used as Proton Pump inhibitorhaving mode of action as it is binds irreversibly to H+/K+ATPase(Proton Pump) and suppresses the secretion of acid.

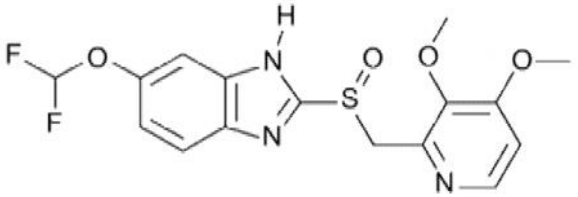

Fig 2: Structure of Pantoprazole

A new stability indicating reversed-phase high performance liquid chromatography method was developed for assay of Domperidone and Pantoprazolein tablets. The validation of method carried out using ICH guidelines. The developed methodwas accurate, precise, economic, fast, and selective for simultaneous determination of DOM and PTZ in combined tablet formulation. The method gave good resolution for drugs. (1-2).

2. Materials and Methods

Chemicals and Reagents:

Domperidone (5gms) obtained as gift sample by Leben Pvt. Ltd. Akola, India and its claimed purity was 99.3% and Pantoprazole (5gms) supplied as gift sample by Taj Pharmaceuitical Limited Mumbai, India and have 99.5% purity. The Duexis (Domperidone & Pantoprazole) as a marketed formulation used which containing Domperidone -30 mg, Pantoprazole -40 mgmanufactured by AlkemPharmapvt. Ltd. HPLC grade Methanol, Water, Acetonitrile, Ortho Phosphoric Acid (OPA)was procured. Hydrochloric acid (35% GR), Hydrogen peroxide, Sodium hydroxide was procured from Merck, India

Instrumentation:

The HPLC analysis was performed using Younglin (S.KGradient) equipped with UV 730D detector,column C18 cosmosil (4.6 ×250mm, 5µm)and the output signals were monitor and processed using data processor Autochro-3000and UV Spectrophotometer(Shimadzu,Model-1700) was used.Ultrasonicator (RC-SYSTEMMU-17000) to sonicate mobile phase and samples. Analytical balance model DS-852JSERIES use to weigh Standard and sample drugs, pH of mobile phase was adjusted by using Digi sun digital pH meter.

Experimental work

Chromatography:

The separation was achieved by using Younglin (S. K Gradient) System with C18 cosmosil(4.6 ×250mm, 5µm)column. The mobile phase consists of a mixture of Methanol: Water (60:40 v/v) pH adjusted to 2.5 with 0.05% of OPA. The mobile phase was set at a flow rate 0.7ml/min. Wavelength selected for the determination of 285nm according to observation.

Standard solutions

Stock solution for Domperidone&Pantoprazole:

30 mg DOM working standard and 10 mg PTZ working standard were transfer to 50.0 ml volumetric flask. Add 40 ml methanol (HPLC Grade) sonicated to dissolve. The solution was cooled to normal temperature and make up the volume with methanol (HPLC Grade) which gives final concentrations of DOM and PTZ 600.0µg/ml and 800.0µg/ml respectively.

Working Standard Solution:

Take 0.05 ml of PTZ stock solution and 0.5 ml of DOM stock solution in a 10.0 ml volumetric flask and make up the volume up to the mark by using mobile phase to get 8µg/ml PTZ & 6 µg/ml DOM.

Sample Solution:

Take the powdered tablet of about 441 mg of DOM and PTZ in 50 ml of saperate volumetric flask add sufficient mobile phase, sonicate for 15 min, make up the volume up to the mark with mobile phase and filtered it with 0.24µ porous size filter to get 600.0µg/ml and 200.0 µg/ml of DOM and PTZ respectively. Take 0.05ml PTZ and 0.5 DOM from above prepared solution of PTZ and DOM in a 10.0 ml volumetric flask and make up the volume up to the mark with mobile phase to get 1 µg/ml PTZ&30.0µg/ml DOM.

Method Validation (3-8)

Validation of the analytical method is the process that was established by laboratory studies in which the performance characteristics of the method meet the requirements for the intended analytical application. The developed RP-HPLC method was validated according to International Conference on Harmonization (ICH) guidelines. The RP-HPLC method was validated for the parameters like linearity, accuracy, precision and ruggedness, robustness limit of detection (LOD) and limit of quantification (LOQ).

Linearity Studies:

From the stock standard solution, aliquots portions (0.5 – 2.5 ml of DOM and 0.05 – 0.25 of PTZ) were transferred into a series of 10.0 mL volumetric flasks and diluted up to the mark with mobile phase to obtain final concentration in the range of 30-150 µg/mL for DOM and 1-5µg/mlfor PTZ.A constant volume of 20.0 µl of each sample was injected and calibration curve was constructed by plotting the peak area versus the drug concentration.

System Suitability Test:

It is apharmacopoeia requirement used to verify the resolution and reproducibility of the chromatographic system used in analysis study, use to verify the sutability of the resolution and reproducibility of chromatographic system use for analysis. The tests were performed by collecting data from five replicate injections of standard solutions.

10 mg DOM working standard and 10 mg PTZ working standard were transfer to 10.0 ml volumetric flask. Add 5 ml methanol (HPLC Grade) sonicated to dissolve The solution was cooled to normal temperature and make up the volume with methanol (HPLC Grade) which gives final concentrations of DOM and PTZ 1000.0µg/ml and 1000.0µg/ml respectively. Pipette out 0.1 ml of these solutions into 10.0 ml volumetric flasks separately and diluted up to the mark with mobile phase.

Filtered mobile phase was allowed to equilibrate with stationary phase until steady baseline was obtained. A 20.0µl std. drug solution was injected which was made in five replicates and the system suitability parameters were recorded.

Method Validation

Accuracy and precision:

10 tablets were weighed and powdered for analysis of the same was carried out. Standard addition method was used for recovery studies. The amount of DOM and PTZ were added at to reanalyzed sample at three different concentration levels i.e. 80%, 100% and 120% of assay concentration and percent recoveries were calculated. Now we have to make three different aliquot i.e. 0.8, 1.0, 1.2 ml by pipette out 1 ml of the sample solution and transfer to 10.0 ml volumetric flask separately of DOM and PTZ, All the solutions were filtered through 0.45 µm Nylon-66 filter and injected into HPLC system. The percent recovery was then calculated by using formula.

Precision is the measure of closeness of the data values to each other for a number of measurements under the same analytical conditions.

Precision of the assay was determined by repeatability (intra-day) and intermediate precision (inter-day).

$$\% \text{ Recovery} = \frac{Ew - B}{C} \times 100$$

Where, Ew = Total drug estimated (mg)

B= Amount of drug contorted DOM by pre-analyzed tablet powder (mg)

C= Weight of pure drug added (mg)

Ruggedness and Robustness:

Ruggedness was evaluated by performing assay of the formulations by different analyst, keeping the other parameters unchanged and in parallel; the chromatographic profile was observed and recorded.The Robustness of the method was evaluated by changing the flow rate by ± 10%, by changing the wavelength by ± 2nm, system suitability was done for each condition. The peak area obtained with each solution was measured and % RSD was calculated.

Linearity and Range:

The concentration ranges 1-6µg/ml for PTZ and 8-16µg/ml for DOM were selected as linearity range.

Forced degradation study (Stress studies) of DOM and PTZ: Forced degradation study was carried out to decide whether the analytical method for assay was stability indicating. The tablets of DOM and PTZ were subjected to various stress conditions to conduct forced degradation studies. Forced degradation was carried out under the conditions of acid/base hydrolysis, oxidation, photolytic and thermal degradation in accordance with ICH Q1A (R2). For deciding that whether the analytical method for the assay was stability indicating, tablets of DOM and PTZ were subjected to various stress conditions to conduct forced degradation studies. Stress studies were carried out under the conditions of acid/base hydrolysis, oxidation, photolytic and thermal degradation in accordance with ICH Q1A (R2). Several trials with different severity of each stressed condition were conducted, so that upto 10-30% degradation was achieved.

$$\% \text{ Degradation} = \frac{\text{Area of unstressed} - \text{Area of stressed}}{\text{Area of unstressed}} \times 100$$

Acid Degradation:

Take finally powdered tablet equivalent to 800 mg of DOM and 27 mg of PTZ transfer to 10.0 ml volumetric flask. Then add 0.1 N HCL was added to make up the volume and

refluxed on heating mantle for 45min at 65 ºC.

Basic Degradation:

Take finally powdered tablet equivalent to 800 mg of DOM and 27 mg of PTZ transfer to 10.0 ml volumetric flask. Then add 0.1 N NaOH was added to make up the volume and refluxed on heating mantle for 45min at 65 ºC.

Oxidative/ Peroxide Degradation:

Take finally powdered tablet equivalent to 800 mg of DOM and 27 mg of PTZ transfer to 10.0 ml volumetric flask. Then add 3% H_2O_2 was added to make up the volume and refluxed on heating mantle for 45min at 65 ºC.

Neutral Degradation:

Take finally powdered tablet equivalent to 800 mg of DOM and 27 mg of PTZ transfer to 10.0 ml volumetric flask.Refluxed on heating mantle for 45min at 65 ºC.

In order to establish whether the analytical method for the assay was stability indicating, tablets of DOM and PTZ were subjected to various stress conditions to conduct forced degradation studies. Stress studies were carried out under the conditions of acid/base hydrolysis, oxidationand reduction in accordance with ICH Q1A (R2) and USFDA guidelines. Several trials with different severity of each stressed condition were conducted, so that up to 10-30% degradation was achieved.

3. Results and Discussion

The aim of the present investigation is to develop a sensitive, precise and accurate high-performance liquid chromatographic method for the determination of Domperidone and Pantoprazole in tablet dosage form for developing the method varying one parameter at a time and keeping all other conditions constant. Method development consists of selecting the appropriate wavelength and choice of stationary and mobile phases. Based on the nature and solubility characteristics of Domperidone and Pantoprazole, reverse phase mode of HPLC was selected for chromatography. Among different RP-HPLC stationary phases, Cosmosil C18 column (4.6 ×250mm, 5µm) was found to be optimum. In order to get good peak with proper separation from interfering peaks carried out a number of trials by varying the composition of mobile phase, pH and its flow rate. To have a proper separation of the drugs under isocratic conditions, mixtures of solvents like methanol, water with different buffers in different combinations were tested as mobile phase. A mixture of Methanol: Water (60:40 v/v) pH adjusted to 2.5 with 0.05% of OPA. The mobile phase was set at a flow rate 0.7ml/min. Wavelength selected for the determination of 285nm. Under these conditions, the analytic peaks of both drugs were well resolved. The proposed RP-HPLC method was successfully used for the simultaneous determination of the Domperidone and Pantoprazole.

System suitability:

System suitability test was applied to representative chromatograms for various parameters such as tailing factor and number of theoretical plates was determined. The results reported (Table 1 and Fig 3) indicated that the asymmetrical factor was not more than 2.0, theoretical plate not less than 2000 for DOM, PTZ and the % RSD of peak area was not more than 2.0, which full-fills proper suitability of the proposed RP-HPLC method during all validation parameters. Thus, the system meets suitable criteria.

Table 1: System suitability parameter

Parameter	DOM	PTZ
Retention time	2.3	5.6833
peak area	3651.8	822.9
Tailing factor	1.2	1.1667
Theoretical plate	3650	7960.5
%RSD	0.47	0.32

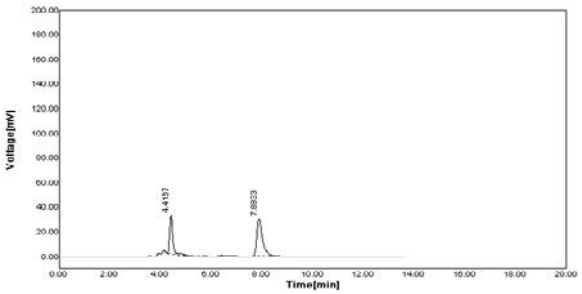

Fig 3: Chromatogram showing separation of DOM & PTZ

Linearity: Linearity was established by least squares linear regression analysis of the calibration curve. The correlation coefficient (r2) was calculated, and it was 0.999 which is well within the acceptance criteria. The results are shown in Table 2. The concentration was found to be proportional to the area, and the response of the detector was determined to be linear over the range for DOM & PTZ was found to be 30-150µg/ml&1-5µg/ml(Fig. 4. & Fig. 5).

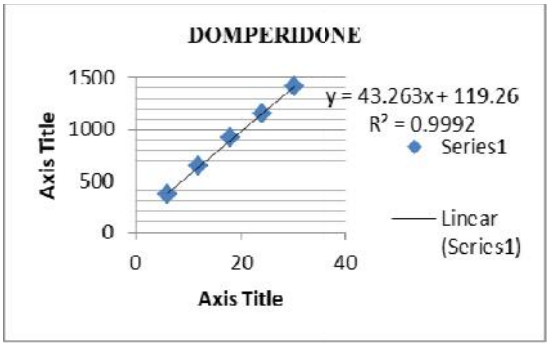

Fig 4: Linearity graph for DOM

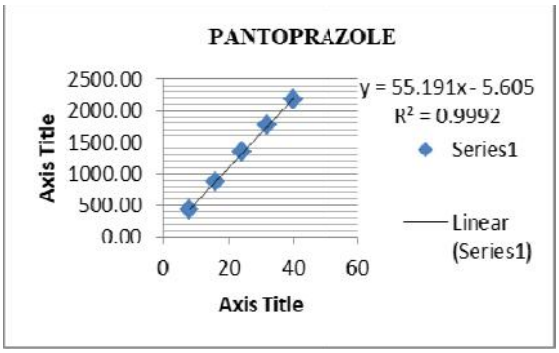

Fig 5: Linearity graph for PTZ

Accuracy: Accuracy was studied by recovery study using standard addition method. The accuracy was determined by measuring the recovery of DOM & PTZ at three different levels (80%, 100% and 120 %). The mean % amount found was 99.82 (DPD) &99.91 (PTZ) with % RSD values was NMT 2.0% indicates the developed method was successfully applied for analysis of marketed formulation. All the results found were in good agreement with the label content of marketed formulation. The result shown in table no. 3**.**

Precision: Precision was determined as retention time and peak areas was seen in both intra and inter day precision studies with a %RSD(NMT than 2%)which was in agreement with system suitability. Therefore, the proposed HPLC method for the determination of DOM and PTZ in a tablet was found to be sufficiently precise.

Ruggedness and Robustness:

Ruggedness was evaluated by performing assay of the formulations by different analyst by injecting four consecutive injections of the sample atworking concentration from the same homogeneous mixture of tablets. This study showed required criteria also shows % assay for both the drugs which indicate that the method developed is rugged, result shown in Table 6. &the robustness study results of assay of test solution were not affected by varying the conditions. They fully agree with the results obtained under original conditions. The composition of mobile phase, changes in wavelength and flow rate not affectsthe method significantly; hence indicate the method developed was robust, it shown in Table .7.

Forced degradation studies: The chromatograms of the samples of DOM and PTZ subjected to various forced degradation conditions showed well-separated peaks of the actives and the degradation products at different retention times. However, in some conditions, the actives did not show separate peaks of the degradation products, rather a decrease in height and area of the peak was observed. The peaks of the degradation products were identified and compared with that of the standard solution and were found to be well resolved from the peaks. The degradation studies revealed that the sample of DOM and PTZ in combination was more stable against oxidation, photolytic studies, and thermal studies than acid and base degradation.

Acid degradation: Degradation under acidic condition may due to catalysis of ionizable functional group present in the drug molecule. Three degradants were observed for acid condition having % area5.54, 3.39, 13.05respectively. After retention time of PT Zone degradant peak were reported having % area 1.84. In acidic condition DOM degraded higher than PTZ. Degradation result shown in Fig. 6 and Table 8.

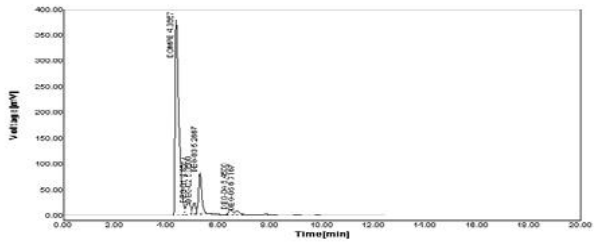

Fig 6: Acid degradation

Base Degradation: Degradation under basic condition may due to catalysis of ion-sable functional group present in the drug molecule three degradants were observed for basic condition having % area 7.41,9.64 & 4.88 but not any more degrading peak were reported in retention time DOM& PTZ respectively. In basic condition DOM degraded higher% degradation. Degradation result shown in Fig. 7 and Table 9.

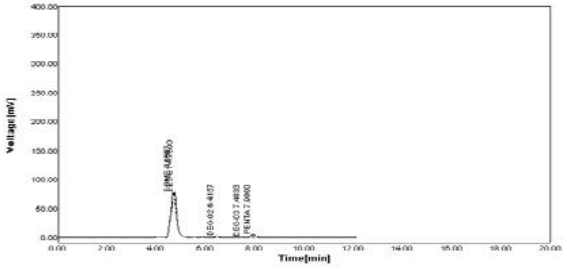

Fig 7: Base degradation

Oxidative degradation:

Degradation under oxidation condition may due to electron transfer mechanism. three degradants were observed for oxidative condition having % area 26.97,9.15,4.79% but not any more degrading peak were reported in retention time of DOM& PTZ respectively. The degradation result shown in Fig. 8 and Table 10.

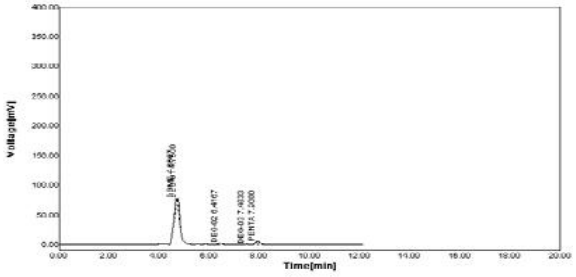

Fig 8: Oxidative degradation

Neutral degradation:

Degradation under neutral condition in which Five degradant were observed after the peak of DOM having % area 48.22% and 4.76 %. and three degrading peaks was reported in retention time of PTZ respectively. The degradation result shown in Fig. 9 and Table 11.

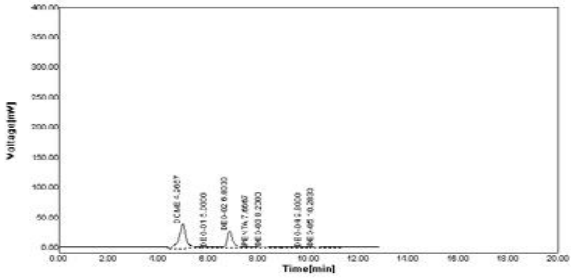

Fig 9: Neutral degradation

4. Conclusion

From the present study it is concluded that, the RP-HPLC method shows the good resolution between DOM and PTZ within the run time of 20 min and was found to be simple,

accurate, sensitive, precise, specific, economical and rapid. The method is very simple and no complicated procedure utilized for sample preparations. As the result indicate that, RP-HPLC method was found to be linear over wider concentration range, it can be applied for routine qualitative and quantitative analysis of DOM and PTZ in bulk and pharmaceutical formulations like tablets. The RP-HPLC method was confirmed as per the ICH guidelines. Both parent drugs and degradation products were well determined using optimized chromatographic conditions which indicate the selective nature of established RP-HPLC method. The RP-HPLC method developed in the present investigation has a stability indicating nature hence the proposed method could be employed for the stability studies on pharmaceutical preparations within pharmaceutical industry.

Table 2: Statistical data of Linearity of DOM & PTZ

Parameter	Domperidone	Pantoprazole
Linearity range (µg/ml)	30-150 µg/ml	1-5ug/ml
Regression equation	Y=43.26x + 119.2	Y=55.19x - 5.605
Correlation coefficient	R =0.999	r2 =0.999
Slope	43.166	55.19
Intercept	119.26	5.605

Table 3: Results of Accuracy of DOM & PTZ

Level of % Recovery	Amount present (mg/tab)		Amount taken (µg/ml)		Amount of Std. Drug Added (µg/ml)		Total Amount Recovered (µg/ml)		%Recovery	
	DOM	PTZ	DOM	PTZ	DOM	PTZ	DOM	PTZ	DOM	PTZ
80%	30	40	116	16	9.6	16	1059.54	1577.39	101.35	99.08
	30	40	116	16	9.6	16	1053.51	1582.21	99.97	99.76
100%	30	40	116	16	12	16	1152.88	1747.85	99.56	98.56
	30	40	116	16	12	16	1146.72	1759.67	97.93	99.90
120%	30	40	116	16	14.4	19.2	1247.74	1911.07	97.82	97.54
	30	40	116	16	14.4	19.2	1256.19	1914.82	99.18	97.89

Table 4: Results of Intraday precision study using tablet

S. No.	Conc.	Area	II	Mean	Amt Found	% Amt Found	SD	%RSD
1	12	631.85	620.25	626.05	11.91	99.25	3.54	0.57
2	18	920.6	906.31	913.45	18.02	100.11	10.10	1.11
3	24	1195.63	1175.76	1175.69	24.13	100.54	14.05	1.20

Table 5: Results of Interday precision study using tablet

S. No.	Conc.	Area	II	Mean	Amt Found	% Amt Found	SD	%RSD
1	16	878.51	885.79	882.15	16.08	16.53	5.15	0.58
2	24	1359.73	1345.26	1352.49	24.60	102.50	10.23	0.76
3	32	1722.89	1743.92	1733.41	31.50	98.44	14.87	0.86

Table 6: Results of Ruggedness Studies

Analyst	Peak area		Amount found (%)		%RSD	
	DOM	PTZ	DOM	PTZ	DOM	PTZ
Analyst 1	3144	371.1	100.0	99.91	1.04	1.75
Analyst 2	3177	375.1	100.9	98.67	1.02	1.39

Table 7: Results of Robustness Studies

Robustness parameter	DOM %RSD	PTZ %RSD
Flow change **0.6** ml	1.21	0.07
Flow change **0.8** ml	1.14	0.11
Composition change (61:39)	1.4	0.13
Composition change (59:41)	1.02	0.12
Wavelength change 253nm	0.97	0.1
Wavelength change 255nm	0.74	0.13

Table 8: Acid Degradation (0.1N HCl)

Name	Retention Time	Peak Area
DOM	4.3667	3925.18
DEG 1	4.8667	293.40
DEG 2	5.0500	179.16
DEG 3	5.2667	690.48
PTZ	6.4500	100.27
DEG 1	6.7167	97.23

Table 9: Base Degradation (0.1N NaOH)

Name	Retention Time	Peak Area
DOM	4.1667	3111.11
DEG-01	4.4167	7027.42
DEG-02	5.1667	1078.44
DEG-03	5.3167	1402.16
PTZ	5.8833	1221.75

Table 10: Oxidative Degradation (3%H_2O_2)

Name	Retention Time	Peak Area
DOM	4.6667	96.74
DEG-01	4.7500	83.21
DEG-02	6.4167	28.22
DEG-03	7.4833	14.78
PTZ	7.9000	85.55

Table 11: Neutral Degradation (Water)

Name	Retention Time	Peak Area
DOM	4.9667	792.40
DEG-01	6.0000	78.2233
DEG-02	6.8333	484.82
PTZ	7.6667	36.9924
DEG-01	8.2000	109.75
DEG-02	9.8000	65.1535
DEG-03	10.283	75.9599

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