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Method Development and Its Validation for Simultaneous Estimation of Domperidone and Esomeprazole by RP-HPLC in Combination Tablet Dosage Form

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ABSTRACT:

A simple and validated reverse phase high performance liquid chromatography (RP-HPLC) method was developed for simultaneous estimation of Esomeprazole and Domperidone. Different HPLC Chromatographic conditions were used to find out the optimum chromatographic condition for best elution of drugs. Good chromatographic separation was achieved on Develosil ODS HG-5 RP C_{18} (15cmX4.6mm, 5µm Particle size), analytical column using a mixture of Potassium dihydrogen phosphate buffer pH: acetonitrile in the ratio of 45:55 v/v used as mobile phase at the flow rate of 1 ml/min and detector wavelength at 284nm. The validation of the proposed method was carried out for specificity, linearity and range, accuracy, precision, limit of detection and limit of quantification. Linearity range was found to be 0-140 µg/ml and 0-150 µg/ml with correlation coefficients of 0.995 & 0.994 and retention time of 2.59 and 3.85 min for Domperidone and Esomeprazole respectively. The LOD was found to be 0.341 µg/ml and 2.031 µg/ml and LOQ was found to be 1.023 µg/ml and 6.093 µg/ml respectively. The result shows the developed method is yet another suitable method for assay and stability studies which can help in the analysis of Domperidone & Esomeprazole in different formulations.

1. INTRODUCTION:

Esomeprazole magnesium trihydrate (Andersson et al., 2001) (ESO) is chemically bis (5-methoxy-2-[(S)-[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1-H-benzimidazole-1-yl) magnesium trihydrate Figure 1, a compound that inhibits gastric acid secretion. Esomeprazole is cost effective in the treatment of gastric oesophageal reflux diseases. Esomeprazole is the S-isomer of omeprazole, the first single optical isomer proton pump inhibitor, generally provides better acid control than current racemic proton pump inhibitors and has a favorable pharmacokinetic profile relative to omeprazole (Scott et al., 2002, Prabu et al., 2008)

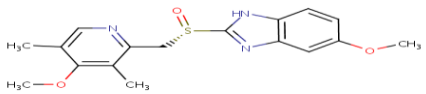

Figure 1: Structure of Esomeprazole

Domperidone (DOM) is chemically 5-Chloro-1-[1-[3-(2-oxo-1, 3-dihydrobenzimi-dazol-1-yl]-4-piperidyl]-1, 3- dihydrobenz imidazol-2-one maleate Figure 2. Domperidone acts as a gastrointestinal emptying (delayed adjunct and peristaltic stimulant).

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The gastroprokinetic property of domperidone is related to its peripheral dopamine receptor blocking properties (Shradha et al 2015). Domperidone exerts its effect at peripheral D_2 receptors in the GI tract; the CTZ, which is outside the blood brain barrier; and the pituitary. It has antiemetic property similar to metoclopramide and neuroleptic drugs. Unlike these drugs, however, domperidone does not readily cross the blood brain barrier and seldom causes extra pyramidal side effects (Vasantharaju et al.,2012). It is a potent gastrokinetic agent causing faster gastric emptying. The combination of domperidone with lansoprazole or esomeprazole is used to treat GERD (Sharma et al., 2011).

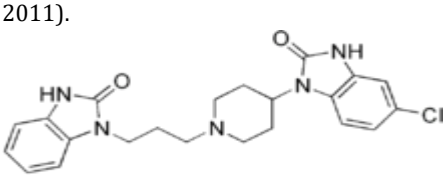

Figure 2: Structure of Domperidone

This work focuses on method development and its validation for simultaneous estimation of Esomeprazole and Domperidone by RP-HPLC method in combined dosage form. Different HPLC Chromatographic conditions were used to find out the optimum chromatographic condition for best elution of drugs.

2. MATERIALS & METHODS

2.1 Instruments Used

UV-Visible double beam spectrophotometer-Elico India, HPLC-Hitachi LaChrome, Ultra sonicator-Entrech electronics limited, Melting point apparatus.

2.2. Chemicals / Reagents Used

Domperidone and Esomeprazole was obtained from Micro Labs Limited. Tablets of Brand name ESOFAG-D cap were obtained from Flemingo. Double distilled water, Sodium Hydroxide, Potassium dihydrogen orthophosphate and orthophosphoric acid was obtained from Sd fine-Chem ltd; Mumbai, Methanol and Acetonitrile was obtained from Loba Chem; Mumbai.

2.3 Method Development and Its Validation

2.3.1 Selection of wavelength

The λ_{max} of the two ingredients i.e. Domperidone and Esomeprazole, were found to be 284 nm and 301 nm respectively in methanol as solvent system.the isobestic point for the drugs were found at 284 nm.

2.3.2 Preparation of standard solution of Domperidone

10 mg of Domperidone was weighed accurately and transferred into 100 ml volumetric flask. About 10 ml of HPLC grade methanol was added and sonicated to dissolve. The volume was made up to the mark with same solvent. The final solution contained about 100 µg/ml of Domperidone Figure 3.

2.3.3 Preparation of standard solution of Esomeprazole

10 mg of Esomeprazole was weighed accurately and transferred into 100 ml volumetric flask. About 10 ml of HPLC grade methanol was added and sonicated to dissolve. The volume was made up to the mark with same solvent. The final solution contained about 100 µg/ml of Esomeprazole Figure 4.

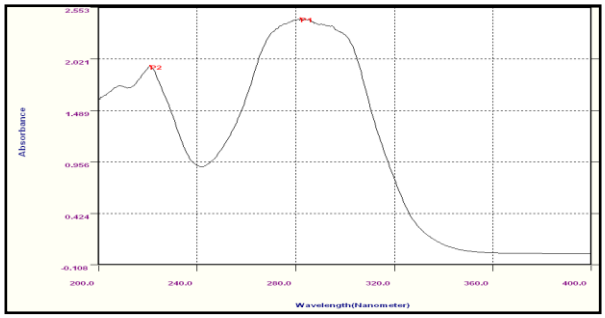

Figure 3: UV Spectrum of DOMPERIDONE

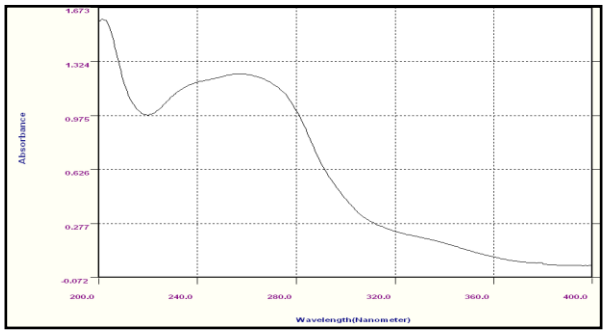

Figure 4: UV Spectrum of ESOMEPRAZOLE

2.3.4 Preparation of mix. standard solution of Domperidone and Esomeprazole

Accurately weighed 30 mg of Domperidone and 40 mg of Esomeprazole were transferred to 100 ml volumetric flask. About 40 ml of HPLC grade methanol was added and sonicated to dissolve. The volume was made up to mark with same solvent. Then 10 ml of the above solution was diluted to 100 ml with the solvent system. The resultant solution was filtered through a 0.45 µm membrane filter and degassed under ultrasonic bath prior to use. From the above standard solution several working standard solutions are prepared by serial dilution technique.

2.3.5 Initialization of the instrument

The HPLC instrument was switched on. The column was washed with HPLC water for 45 minutes. The column was then saturated with mobile phase for 45 minute. The mobile phase was run to find the peaks. After 20 minutes the standard drug solution was injected in HPLC.

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2.3.6 Different chromatographic conditions used and their Optimizations

The different HPLC chromatographic conditions were used to find out the optimum chromatographic condition for best elution of drugs.

Table 1: Chromatographic conditions 1

Mobile phase	Water:ACN(80:20)
Wavelength	284nm
Flow rate	0.8 ml/ min.
Run time	10 min.
Column	Develosil ODS HG-5 RP C_{18}, 5µm 15cmx4.6mm i.d.

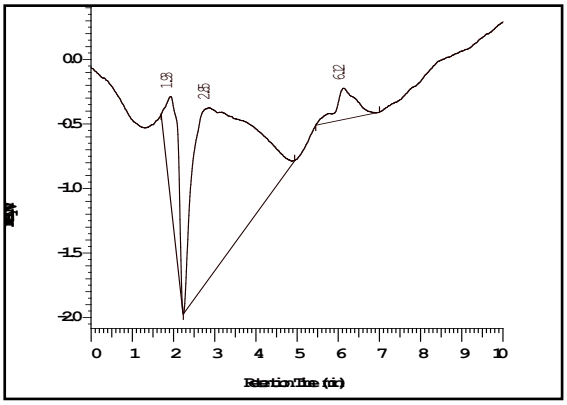

Figure 5: Chromatogram for Condition 1

Results & Discussion:

Figure 5: No peaks were separated and a negative peak was also found. Hence chromatogram was not acceptable.

Table 2: Chromatographic conditions 2

Mobile phase	**Water: Methanol (20:80)**
Wavelength	**284nm**
Flow rate	**0.8 ml/ min.**
Run time	**10 min.**
Column	**Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.**

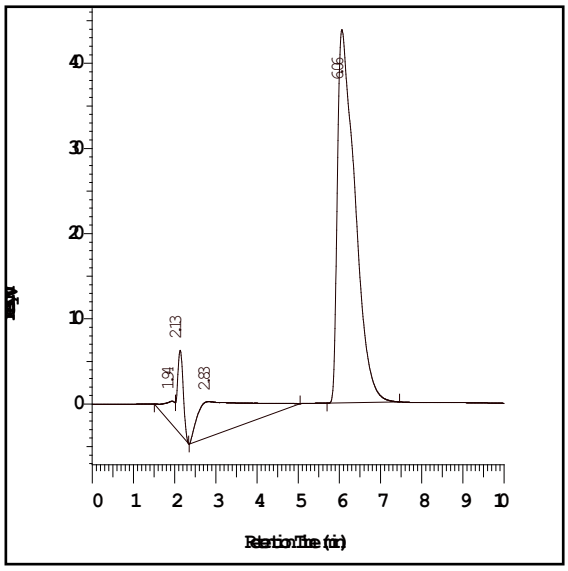

Figure 6: Chromatogram for Condition 2

Results & Discussion:

Resolution and peak shape were low. Peak tailing and a negative peak were found. Hence chromatogram was not acceptable.

Table 3: Chromatographic conditions 2

Mobile phase	Water: Methanol: acetonitrile (10:30:60)
Wavelength	284nm
Flow rate	0.6 ml/ min.
Run time	10 min.
Column	Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.

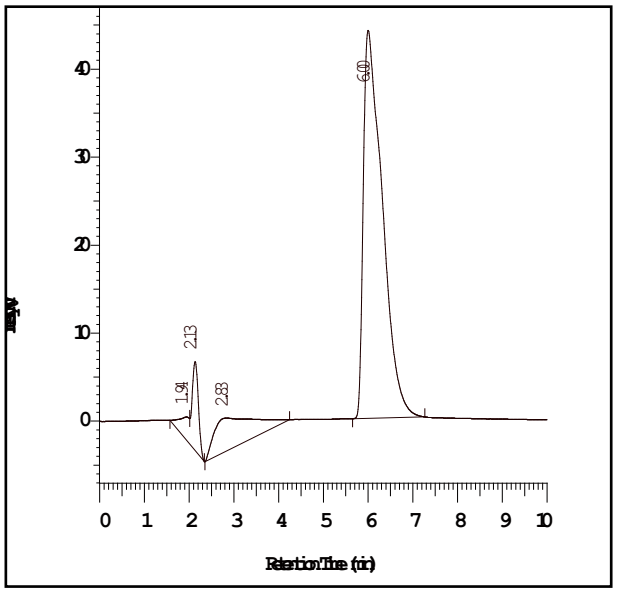

Figure 7: Chromatogram for Condition 3

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Results & Discussion:

Peak separation was not good and also a third peak was found. Hence chromatogram was not acceptable.

Table 4: Chromatographic conditions 4

Mobile phase	Water: Methanol: acetonitrile (10:60:30)
Wavelength	284nm
Flow rate	0.6 ml/ min.
Run time	10 min.
Column	Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.

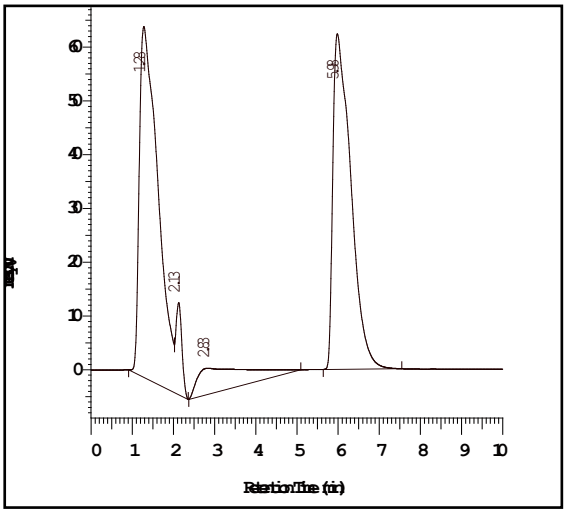

Figure 8: Chromatogram for Condition 4

Results & Discussion:

Peak separation was good but tailing factor found. Hence chromatogram was not acceptable.

Table 5: Chromatographic conditions 5

Mobile phase	Potassium dihydrogen phosphate buffer(0.02 M, pH 3.0): acetonitrile (45:55)
Wavelength	**284nm**
Flow rate	**1.0 ml/ min.**
Run time	**10 min.**
Column	**Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.**

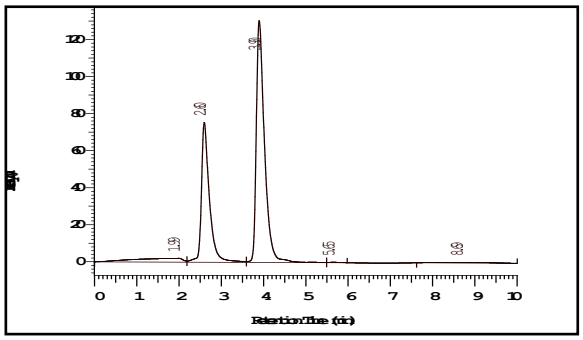

Figure 9: The chromatogram obtained after condition 5, Typical chromatogram of Domperidone (RT=2.60 min) and Esomeprazole (RT= 3.90 min).

Result & Discussion:

Here resolution was good, theoretical plate count and symmetry was appropriate. Also no unwanted little peaks were seen between two peaks. Hence it is acceptable.

Final Result & Discussion: The selected and optimized mobile phase was acetonitrile: potassium dihydrogen phosphate buffer (0.02M, pH 3.0) (55:45v/v) and conditions optimized were: flow rate (1.0 ml/minute), wavelength (284 nm), Run time was 20 min. Here the peaks were separated and showed better resolution, theoretical plate count and symmetry. The proposed chromatographic conditions were found appropriate for the quantitative determination of the drugs.

2.3.7 Preparation of mobile phase

Mobile phase was prepared by taking acetonitrile: potassium dihydrogen phosphate buffer (0.02M, pH 3.0) (55:45v/v). Mobile phase was filtered through 0.45 µm membrane filter and degassed under ultrasonic bath prior to use. The mobile phase was pumped through the column at a flow rate of 1.0 ml/min.

2.3.8 Running the standard solution of Domperidone

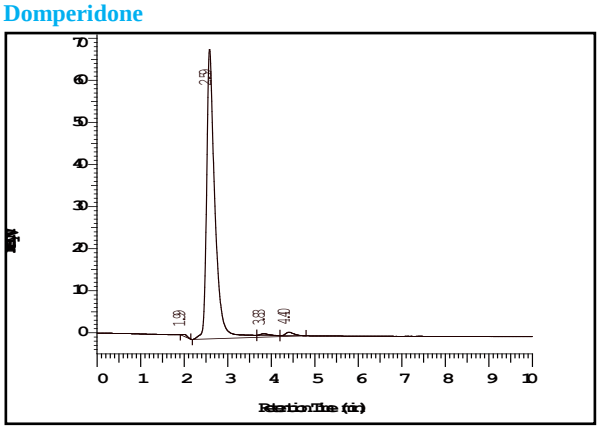

Figure 10: Chromatogram of DOMPERIDONE

Result & Discussion: Retention time was found to be 2.59 min.

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2.3.9. Running the standard solution of Esomeprazole

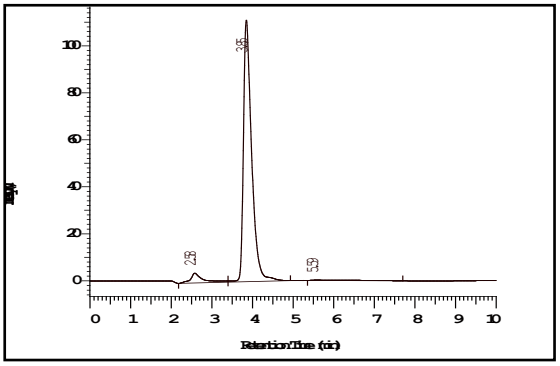

Figure 11: Chromatogram of Esomeprazole

Result & Discussion: Retention time was found to be 3.85 min.

Result & Discussion: The HPLC system was set with the optimized chromatographic conditions to run the standard solution of Domperidone and Esomeprazole for 10 min. The retention time were found to be 2.59 min and 3.85 min respectively.

2.4. Method Validation

2.4.1 Specificity

Preparation and running of synthetic mixture of Domperidone and Esomeprazole

For the specificity of the method the marketed formulations has been taken & the solution was injected into the HPLC system. The chromatograms obtained are shown in Figure 12.

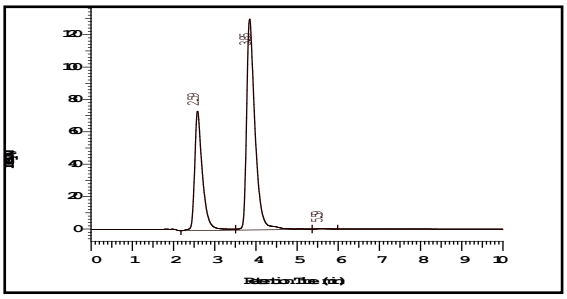

Figure 12: Chromatogram of synthetic mixture

Result and discussion:

No peaks were found at the retention of DOMPERIDONE and ESOMEPRAZOLE. Specificity studies indicating that the excipients did not interfere with the analysis.

2.4.2 Linearity and Range

Method:

Linearity was established by least squares linear regression analysis of the calibration curve. The calibration curves were linear over the concentration range of 0-140 µg/ml for Domperidone and 0-150 µg/ml for Esomeprazole, Peak areas were plotted versus respective concentrations and linear regression analysis was performed on the resultant curves.

Result & Discussion

Linearity range was found to be 0-140 µg/ml for Domperidone and 0-150 µg/ml for Esomeprazole. The correlation coefficients were found to be 0.995 & 0.994, the slopes were found to be 8031 & 41291 and intercept were found to be 10243 & 13551 for Domperidone and Esomeprazole respectively Figure 13 and Figure 14.

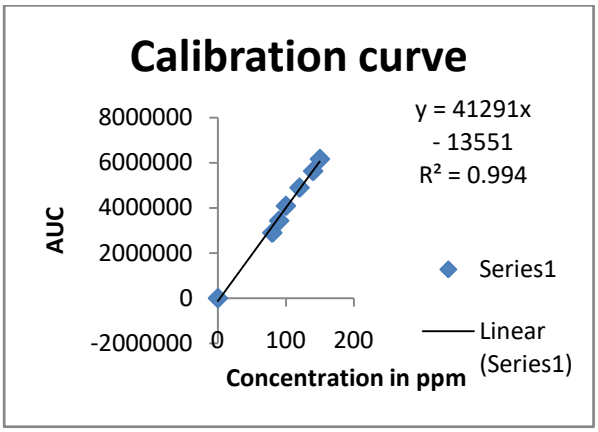

Figure 13: Standard curve for Esomeprazole

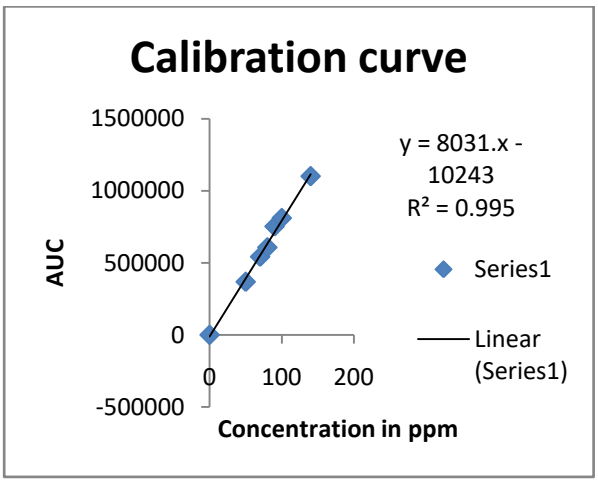

Figure 14: Standard curve for Domperidone

2.4.3 Accuracy

Recovery study: Domperidone

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of DOMPERIDONE were taken and added to the pre-analyzed formulation of concentration 80µg/ml. From that percentage recovery values were calculated. The results were shown in Table-6.

Recovery study: Esomeprazole

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of Esomeprazole to the pre-analyzed formulation of concentration 100µg/ml. From that percentage recovery

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values were calculated. The results were shown in Table-8.

Result & Discussion: The mean recoveries were found to be 99.97, 99.54, 99.57 % for Domperidone and 99.94, 99.76, 99.37% for Esomeprazole. The limit for mean % recovery is 98-102% and as both the values are within the limit, hence it can be said that the proposed method was accurate.

Table.6: Accuracy Readings Domperidone

Sample ID	Concentration (µg/ml)		%Recovery of Pure drug	Statistical Analysis
	Pure drug	Formulation		
S_1 : 80 %	65	80	99.18	Mean= 98.97667% S.D. = 0.200083 % R.S.D.= 0.202152
S_2 : 80 %	65	80	98.78	
S_3 : 80 %	65	80	98.97	
S_4 : 100 %	80	80	99.87	Mean= 99.54% S.D. = 0.33 % R.S.D.= 0.331525
S_5 : 100 %	80	80	99.54	
S_6 : 100 %	80	80	99.21	
S_7 : 120 %	95	80	99.32	Mean= 99.567% S.D. = 0.33 % R.S.D. = 0.331159
S_8 : 120 %	95	80	99.65	
S_9 : 120 %	95	80	99.98	

Table.7: Accuracy Readings for Esomeprazole

Sample ID	Concentration (µg/ml)		%Recovery of Pure drug	Statistical Analysis
	Pure drug	Formulation		
S_1 : 80 %	80	100	99.13	Mean= 98.94667% S.D. = 0.171561 % R.S.D.= 0.1733
S_2 : 80 %	80	100	98.79	
S_3 : 80 %	80	100	98.92	
S_4 : 100 %	100	100	99.72	Mean= 99.76% S.D. = 0.045826 % R.S.D.= 0.0459
S_5 : 100 %	100	100	99.81	
S_6 : 100 %	100	100	99.75	
S_7 : 120 %	120	100	99.36	Mean= 99.37667% S.D. = 0.105987 % R.S.D. = 0.1066
S_8 : 120 %	120	100	99.28	
S_9 : 120 %	120	100	99.49	

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2.4.4 Precision

Repeatability

The precision of each method was ascertained separately from the peak areas obtained by actual determination of six replicates of a fixed amount of drug. Esomeprazole & Domperidone. The percent relative standard deviations were calculated for Esomeprazole & Domperidone are presented in the Table 8 and Table 9.

Table 8: Data showing repeatability analysis for Esomeprazole

HPLC Injection Replicates of acceclofenac	Area
Replicate – 1	**4091306**
Replicate – 2	**4095304**
Replicate – 3	**4100358**
Replicate – 4	**4095236**
Replicate – 5	**4098523**
Average	**4096145**
Standard Deviation	**3476.84**
% RSD	**0.08488**

Table 9: Data showing repeatability analysis for Domperidone

HPLC Injection Replicates of atenolol	Area
Replicate – 1	**811256**
Replicate – 2	**810248**
Replicate – 3	**811563**
Replicate – 4	**811248**
Replicate – 5	**810236**
Average	**810910**
Standard Deviation	**623.075**
% RSD	**0.07684**

Result & Discussion: The repeatability study which was conducted on the solution having the concentration of about 80 µg/ml for Domperidone and 100 µg/ml for Esomeprazole (n =5) showed a RSD of 0.7684% for Domperidone and 0.08488% for Esomeprazole. It was concluded that the analytical technique showed good repeatability.

Intermediate precision

For intra-day studies the drug having concentration value 80%, 100 % & 120% of the target concentration (n = 3), were injected in triplicate into the HPLC system and for inter-day studies the drug at above three concentrations were injected in triplicate into the HPLC system for three days. Data were subjected to statistical treatment for the calculation of SD and RSD. The data are shown in Table 10 and 11.

Result and Discussion:

Intraday and interday studies show that the mean RSD (%) was found to be within acceptance limit (≤2%), so it was concluded that there was no significant difference for the assay, which was tested within day and between days. Hence, method at selected wavelength was found to be precise.

Table 10: Data for Esomeprazole analysis

Conc. Of ESOMEPRAZOLE (API) (µg/ml)	Observed Conc. Of ESOMEPRAZOLE (µg/ml) by the proposed method			
	Intra-Day		**Inter-Day**	
	Mean (n=6)	% RSD	Mean (n=6)	**% RSD**
80	80.04	0.88	80.07	**0.94**
100	100.52	0.34	100.05	**0.37**
120	**119.98**	**0.16**	**120.05**	**0.19**

Table 11: Data for Domperidone analysis

Conc. Of DOMPERIDONE (API) (µg/ml)	Observed Conc. Of DOMPERIDONE (µg/ml) by the proposed method			
	Intra-Day		**Inter-Day**	
	Mean (n=6)	% RSD	Mean (n=6)	**% RSD**
65	65.051	0.75	65.046	**0.74**
80	80.031	0.85	80.084	**0.81**
95	**95.04**	**0.48**	**94.95**	**0.48**

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2.4.5 Limit of detection and Limit of quantification

The detection limit (LOD) and quantitation limit (LOQ) may be expressed as:

L.O.D. = 3.3(SD/S).

L.O.Q. = 10(SD/S)

Where, SD = Standard deviation of the response

S = Slope of the calibration curve

Result & Discussion

The LOD was found to be 0.341 µg/ml and 2.031 µg/ml and LOQ was found to be 1.023 µg/ml and 6.093 µg/ml for Domperidone and Esomeprazole respectively which represents that sensitivity of the method is high Figure 15 and 16.

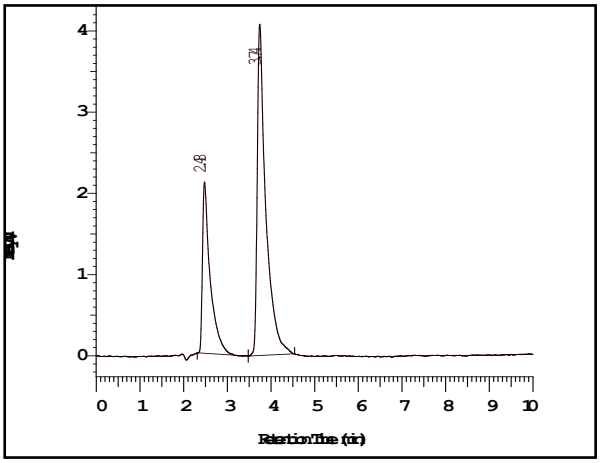

Figure 15: Chromatogram for LOD

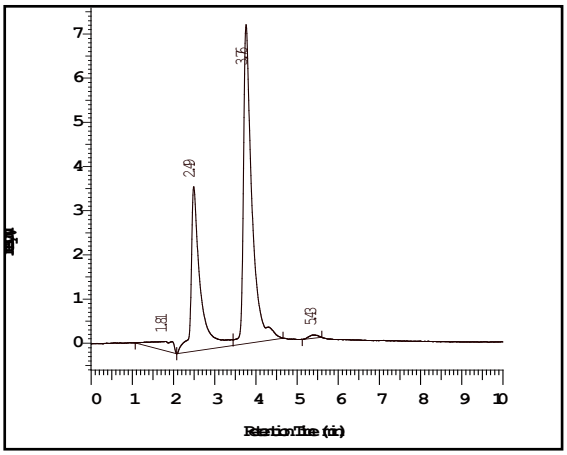

Figure 16: Chromatogram for LOQ

2.4.6 System Suitability Parameter

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. Following system suitability test parameters were established. The data are shown in Table 12.

Table 12: Data of System Suitability Parameter

S.No.	Parameter	Limit	Result
1	Resolution	Rs > 2	9.15
2	Asymmetry	T ≤ 2	DOMPERIDONE=0.12 ESOMEPRAZOLE =0.5
3	Theoretical plate	N > 2000	DOMPERIDONE=3246 ESOMEPRAZOLE= 4693

2.4.7 Assay Of Esomeprazole & Domperidone In Dosage Form:

Estimation of Esomeprazole & Domperidone in Tablet Dosage Form:

Esomeprazole & Domperidone 40mg & 30 mg twenty tablets were taken and the I.P. method was followed to determine the average weight. Above weighed tablets were finally powdered and triturated well. A quantity of powder equivalent to 100 mg of drugs were transferred to 100 ml volumetric flask, and 70 ml of mobile phase was added and solution was sonicated for 15 minutes, there after volume was made up to 100 ml with same solvent. Then 10 ml of the above solution was diluted to 100 ml with mobile phase. The solution was filtered through a membrane filter (0.45 µm) and sonicated to degas. From this stock solution (3.5 ml) was transferred to five different 10 ml volumetric flasks and volume was made up to 10 ml with same solvent system.

The solution prepared was injected in five replicates into the HPLC system and the observations were recorded.

ASSAY:

Assay % =

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \text{Avg. Wt} = \text{mg/tab}$$

Where:

AT = Peak Area of Test obtained with test preparation

AS = Peak Area of Standard obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

DT = Dilution of sample solution

P = Percentage purity of working standard

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Table 13: Recovery Data for estimation Domperidone and Esomeprazole in ESOFAG-D cap

Brand name of Tablets	Labelled amount of Drug (mg) ESOMEPRAZOLE : DOMPERIDONE	Mean (±SD) amount (mg) found by the proposed method (n=6) ESOMEPRAZOLE : DOMPERIDONE	Assay + % RSD ESOMEPRAZOLE : DOMPERIDONE
ESOFAG-D cap	40 : 30	39.10 (±0.498) 29.82 (±0.343)	97.75 (±0.494) 99.40 (±0.349)

Result & Discussion: The amount of drugs in ESOFAG-D cap was found to be 99.40 (±0.349) mg/tab for DOMPERIDONE and 97.75 (±0.494) mg/tab for ESOMEPRAZOLE.

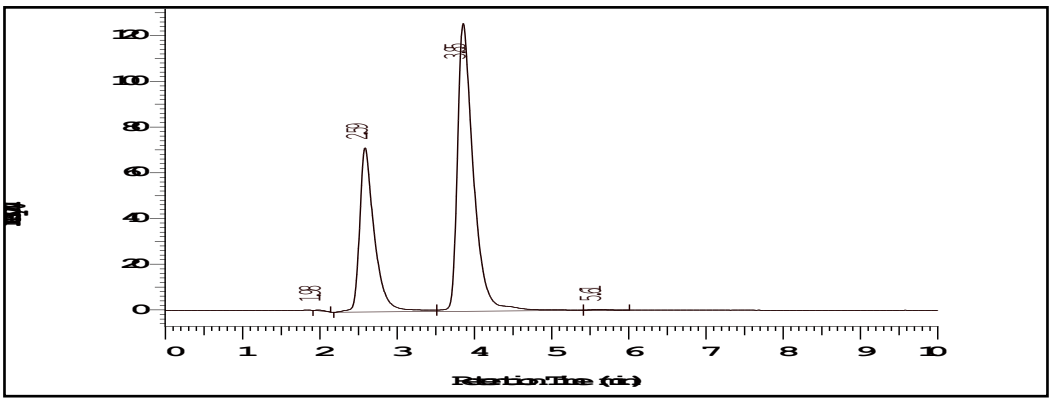

Figure 17: Chromatogram for assay sample-1

3. RESULT & DISCUSSION

To develop a precise, linear, specific & suitable stability indicating RP-HPLC method for analysis of Dompridone & Esomeprazole, different chromatographic conditions were applied & the results observed are presented in the work.

Isocratic elution is simple, requires only one pump & flat baseline separation for easy and reproducible results. So, it was preferred for the current study over gradient elution.

In case of RP-HPLC various columns are available, but here develo Sil, C-18, V size (150mm*4.6mmØ) column was preferred because using this column peak shape, resolution and absorbance were good.

Mobile phase & diluent for preparation of various samples were finalized after studying the solubility of API in different solvents of our disposal (methanol, acetonitrile, dichloromethane, water, 0.1N NaOH, 0.1NHCl). Esomeprazole was found to be insoluble in water and soluble in acetonitrile & methanol. Dompridone was found to be insoluble in water and soluble in methanol & acetontrile.

Detection wavelength was selected after scanning the standard solution of drug over 200 to 800nm. From the UV spectrum of Dompridone & Esomeprazole it is evident that most of the HPLC work can be accomplished in the wavelength range of 215-290 nm conveniently. Further, a flow rate of 1.0 ml/min & an injection volume of 20 µl were found to be the best analysis.

The result shows the developed method is yet another suitable method for assay and stability studies which can help in the analysis of Dompridone & Esomeprazolein different formulations.

The future plan for proceeding in this experiment is to identify the degradation products and their toxicity studies .No matter how much the drug is degraded but the toxicity of the degraded product is of prime importance as this can lead to serious toxic reactions. Sometimes a very small amount of degraded product may render the formulation quite toxic that cannot be taken by the patients.

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4. CONCLUSION

A sensitive & selective stability indicting RP-HPLC method has been developed & validated for the analysis of Dompridone & Esomeprazole API.

Based on peak purity results, obtained from the analysis of samples using described method, it can be concluded that the absence of co-eluting peak along with the main peak of Dompridone & Esomeprazole indicated that the developed method is specific for the estimation of Dompridone & Esomeprazole.

Further the proposed RP-HPLC method has excellent sensitivity, precision and reproducibility.

Even though no attempt has been made to identify the degraded products proposed method can be used as a stability indicating method for assay of Dompridone & Esomeprazole in commercial formulations.

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