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VALIDATED HIGH PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR SIMULTANEOUS ESTIMATION OF MAGALDRATE AND SIMETHICONE IN API AND TABLET DOSAGE FORM AND ITS APPLICATION TO FORCED DEGRADATION STUDIES

Firdous Hassanuddin[*1], G.VIjaya Kumar[1], M.A.Haneef[2]

[1]KGR Institute of technology and management, Sy. No. 419, Rampally, Keesara, Secunderabad, Telangana 501301, India.
[2]Research Scholar, Sri Satya Sai University of Technology and Medical Sciences, Sehore. M.P., 466001.

ABSTRACT

A rapid and precise reverse phase high performance liquid chromatographic method has been developed for the validated of Magaldrate and Simethicone, in its pure form as well as in tablet dosage form. Chromatography was carried out on an Sunfire C18 (4.6×250mm) 5µ column using a mixture of Water and Acetonitrile (60:40% v/v) as the mobile phase at a flow rate of 1.0ml/min, the detection was carried out at 220nm. The retention time of the Simethicone and Magaldrate was 3.0, 3.8±0.02min respectively. The method produces linear responses in the concentration range of 5-25µg/ml of Simethicone and 120-600µg/ml of Magaldrate. The method precision for the determination of assay was below 2.0%RSD. The method is useful in the quality control of bulk and pharmaceutical formulations.

Key words: Simethicone, Magaldrate, PDA Detection, RP-HPLC, Method validation ICH guideline.

INTRODUCTION

Simethicone, is an anti-foaming agent that decreases the surface tension of gas bubbles, causing them to combine into larger bubbles in the stomach that can be passed more easily. Simethicone does not reduce or prevent the formation of gas in the digestive tract, rather, it increases the rate at which it exits the body. However, simethicone can relieve pain caused by gas in the intestines by decreasing foaming, which then allows for easier passing of flatulence [1-5].

Magaldrate

Magaldrate is a common antacid drug that is used for the treatment of duodenal and gastric ulcers, esophagitis from gastroesophageal reflux [6, 7].

The aim of the present investigation is to develop and validate a sensitive, precise and accurate RP-HPLC method for the simultaneous quantification of Magaldrate and Simethicone in bulk and in its combined pharmaceutical formulation. The proposed method is validated as per ICH guidelines.

MATERIALS AND METHOD

Pure standards and Chemicals

Simethicone and Magaldrate were a procured from Sura Labs. Pvt Ltd., Hyderabad. Ortho phosphoric acid, methanol of HPLC grade was purchased from Merck (India) Ltd., Mumbai and HPLC grade water from milli Q water.

Instrumentation

Analysis was carried out using Waters 2695 alliance HPLC system with binary HPLC pump and Waters 2998 PDA detector. Waters Empower2 version software was used for the acquisition of the chromatographic data.

Chromatographic conditions

The HPLC separation and quantification of the Magaldrate and Simethicone were made on the Kromasil C8 Analytical column (250 mm × 4.6mm; 5 µm). An isocratic mobile phase consisting of0.1% OPA: Methanol in the proportion of 55:45v/v at a temperature of 30 °C was the optimized mobile composition and column temperature. The eluate was monitored at 235nm. The

[*]**Corresponding Author Firdous Hassanuddin** E mail: firru72025@gmail.com

mobile was pumped into the column at a flow rate of 1.0mL/min and the run time was 10min. The volume of injection loop was 10µL. Prior to injection of the drug solution the column was equilibrated for at least 15 min with the mobile phase flowing through the system.

Preparation of standard solution:

Accurately weighed and transferred 10 mg of Simethicone and Magaldrate working standard into a 10mL of clean and dry volumetric flasks added about 7mL of Methanol and sonicated to dissolved and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 0.15ml of the Simethicone and 3.6mL of the Magaldrate stock solutions into a 10mL volumetric flask and dilute up to the mark with Methanol.

PREPARATION OF MOBILE PHASE

Preparation of mobile phase

Accurately measured 600ml (60%) of Water, 400ml of Acetonitrile (40%) were mixed and degassed with digital ultra-sonicated for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation

The Mobile phase was used as the diluent.

System Suitability Studies

System suitability for chromatographic separation was checked on each day of validation to evaluate the components of the analytical system in order to show that the performance of the system meet the standards required by the method. Mixed standard solution of Ranitidine, Domperidone and Simethicone solution was injected in six replicates and system suitability parameters were determined System suitability parameters established for the developed method include number of theoretical plates, resolution and tailing factor.

Specificity

The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components. Analytical method was tested for specificity to measure accurately quantities Simethicone and Magaldrate in drug product.

Linearity and Range

The linearity was established by least squares linear regression analysis of the calibration curve for Malgadrate and Simethicone standard solutions by plotting the concentrations of the compound versus peak area response.

Accuracy and Precision

The accuracy of the method was determined by recovery experiments. The recovery studies were carried out 3 times. The percentage recovery and standard deviation of the percentage recovery were calculated. From the data obtained, added recoveries of standard drugs were found to be accurate. The precision of the method was demonstrated by inter-day and intra-day variation studies. In the intraday studies, six repeated injections of standard and sample solutions were made and the response factor of drug peaks and percentage RSD were calculated. In the inter-day variation studies, six repeated injections of standard and sample solutions were made for three consecutive days and response factor of drugs peaks and percentage RSD were calculated.

Robustness

Robustness of the method was determined by making slight changes in the chromatographic conditions. It was observed that there were no marked changes in the chromatograms which demonstrated that the RP-HPLC method developed is robust. The results are shown in below table.

Limit of quantification (LOQ) and detection (LOD)

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.

Simethicone=LOQ=10×9373/43950 =2.1µg/ml**,**
Magaldrate LOQ =10×55482/8277 =67.0µg/ml
Simethicone LOD=3.3×9373/43950 =0.7µg/ml
Magaldrate LOD =3.3×55482/8277=22.1µg/ml

RESULTS AND DISCUSSION

System Suitability Studies

The column efficiency, resolution and tailing factor were calculated for the standard solutions (Table 1).The values obtained demonstrated the suitability of the system for the analysis of this drug combinations, system suitability parameters may fall within ± 2%Relative standard deviation range during routine performance of the method.

Linearity and range

The range of linearity of the method was 120-600 mcg/mL for Magaldrate 5-25mcg/mL for for Simethicone. The calibration curve was constructed by plotting response factor against concentration of drugs. The slope and intercept value for calibration curve was Y = 43950x + 8388 (R^2=0.9998) for simethicone Y = 8277.x + 10151 (R^2=0.9999) for Magaldrate. The results shows an excellent correlation exists between peak area and concentration of Malgadrate and Simethicone within concentration range indicated above. The results for calibration data are shown in Table 2and calibration curves are given in Figure 4, 5 & Table 5& 6.

Accuracy and Precision

The results of accuracy of the method were determined by recovery experiments. The percentage recovery and standard deviation of the percentage recovery were calculated. From the data obtained, added recoveries of standard drugs were found to be accurate (Tables 3, 4& 5).

The precision of the method was demonstrated

By inter-day and intra-day variation studies. In the intraday studies, six repeated injections of standard and sample solutions were made and the response factor of drug and percentage RSD were calculated. In the inter-day variation studies, six repeated injections of standard and sample solutions were made for three consecutive days and response factor of drug and percentage RSD were calculated. The chromatograms of three different levels shown in Figure 7, 8&9. From the results, the developed RP-HPLC method was considered to be precise (Table6).

Acceptance criteria

%RSD of Six different sample solutions should not more than 2 Table:

FORCED DEGRADATION STUDIES

Acid degradation

Degradation was observed by the additon of 0.5N HCl

Alkaline degradation

Degradation was observed by the additon of 0.5N NaOH

Thermal degradation

Degradation was observed when the sample solution was kept under heat at 60-80^0 C for 3hours.

Peroxide degradation

Degradation was observed by the additon of 3% H_2O_2

Photolytic degradation

Degradation was observed by sunlight exposre.

Table 1. Results for Robustness -Simethicone

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 0.9mL/min	658211	3.006	8793	1.2
Less Flow rate of 0.8mL/min	621077	3.441	7269	1.3
More Flow rate of 1.0mL/min More Flow rate of 0.9mL/min	642190	2.663	9446	1.2
Less organic phase	542402	3.185	8126	1.1
More organic phase	642112	2.867	5854	1.3

Table 2. Results for Robustness-Magaldrate

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 0.9mL/min	429069	3.853	5224	1.59
Less Flow rate of 0.8mL/min	472673	4.426	6328	1.58
More Flow rate of 1.0mL/min	392497	3.415	6217	1.54
Less organic phase	391379	4.291	6996	1.61
More organic phase	391703	3.583	6120	1.50

Table 3. System suitability data of Simethicone

S.No	Peak Name	RT	Area (µV*sec)	USP Plate Count	USP Tailing
1	Simethicone	3.008	658263	7462	1.2
2	Simethicone	3.009	658264	8264	1.1
3	Simethicone	3.008	653426	6627	1.2
4	Simethicone	3.010	653058	7264	1.1
5	Simethicone	3.006	657393	6645	1.1
Mean			656080.8		
Std. Dev.			2618.946		
% RSD			0.39918		

Table 4. System suitability data of Magaldrate

S.No	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Magaldrate	3.857	3028176	381011	9583	1.1
2	Magaldrate	3.859	3018373	381645	8927	1.2
3	Magaldrate	3.857	3018462	381663	8465	1.1
4	Magaldrate	3.861	3081711	381746	9222	1.2
5	Magaldrate	3.853	3075143	381193	8462	1.1

Mean			3044373			
Std. Dev.			31427.07			
% RSD			1.0323			

Table 5. Linearity Data of Simethicone

Concentration Level (%)	Concentration µg/ml	Average Peak Area
33.3	5	230247
66.6	10	462332
100	15	659905
133.3	20	892989
166.6	25	1101075

Table 6. Linearity data of Magaldrate

Concentration Level (%)	Concentration µg/ml	Average Peak Area
33.3	120	1215225
66.6	240	2135937
100	360	3020839
133.3	480	4078841
166.6	600	5058145

Table 7. The accuracy results for Magaldrate

%Concentration (at specification Level)	Peak Area	Amount Added (µg/mL)	Amount Found (µg/mL)	% Recovery	Mean Recovery
50%	209357	180	179.9	99.7%	99%
100%	420697.7	360	359.8	99%	
150%	631550.7	540	539.8	99%	

Table 8. The accuracy results for Simethicone

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	331938	7.5	7.3	99.88	100.166
100%	658274	15	14.7	98.89	
150%	970963	22.5	22.2	101	

Table 9. Results of Intermediate precision Day 2 for Simethicone

S.No	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate count	USP Tailing
1	Simethicone	3.006	648822	61847	6983	1.1
2	Simethicone	3.008	640863	59882	7728	1.2
3	Simethicone	3.008	643382	60774	9576	1.1
4	Simethicone	3.007	641884	58928	8275	1.2
5	Simethicone	3.007	647822	61483	9837	1.1
6	Simethicone	3.005	649181	60928	8744	1.2
Mean			645325.7			
Std. Dev.			3711.009			
% RSD			0.57506			

Table 10. Results of Intermediate precision Day 2 for Magaldrate

S.No	Peak Name	RT	Area (V*sec)	Height (µV)	USP Plate count	USP Tailing
1	Magaldrate	3.853	3075833	389911	7039	1.1
2	Magaldrate	3.857	3029583	379019	9857	1.2
3	Magaldrate	3.854	3021991	381875	7881	1.1
4	Magaldrate	3.855	3022485	391099	7902	1.2
5	Magaldrate	3.854	3085833	389222	9285	1.1
6	Magaldrate	3.853	3019482	391184	8955	1.2

Table 11. Results of degradation studies

S. no	Type of degradation	Weight of sample (µg/ml)	Area of sample		Assay content (% w/w)	
			Simethicone	Magaldrate	Simethicone	Magaldrate
1	Acid (0.5N HCl)	15µg/ml of Simethicone and 360µg/ml of Magaldrate	636644	2891741	95.2%	96.6%
2	Base (0.5N NaOH)	15µg/ml of Simethicone and 360µg/ml of Magaldrate	639967	2878174	95.8%	96.2%
3	Peroxide (3% H_20_2)	15µg/ml of Simethicone and 360µg/ml of Magaldrate	629573	2899471	94.2%	96.9%
4	Thermal (at 60^0 - 80^0c)	15µg/ml of Simethicone and 360µg/ml of Magaldrate	649241	2794721	97.2%	93.4%
5	Photolytic (sunlight)	15µg/ml of Simethicone and 360µg/ml of Magaldrate	605937	2811773	90.6%	94.0%

Fig 1. Chemical structure of Simethicone

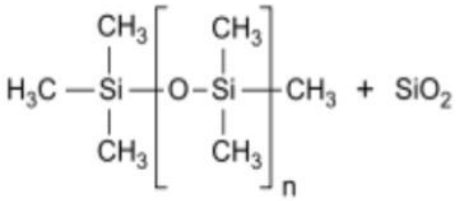


Fig 2. Chemical structure of Magaldrate

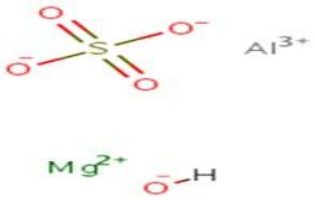


Fig 3. Typical chromatogram of mixed standard solution

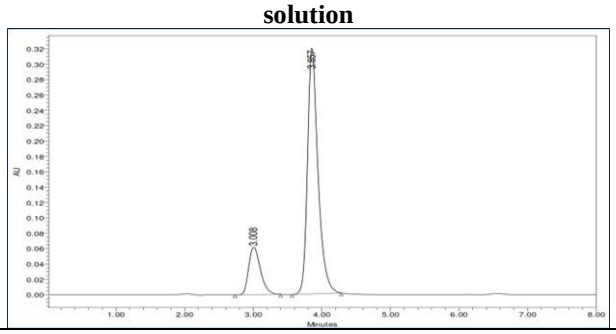


Fig 4. Calibration graph of Simethicone

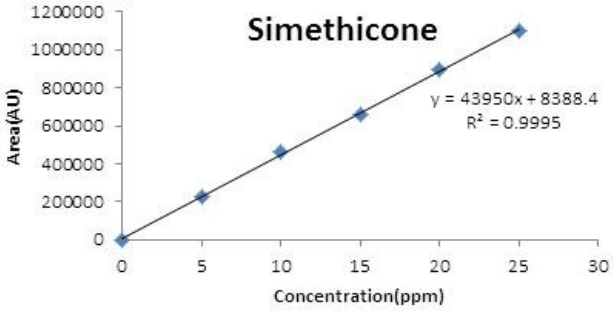


Fig 5. Calibration graph of Magaldrate

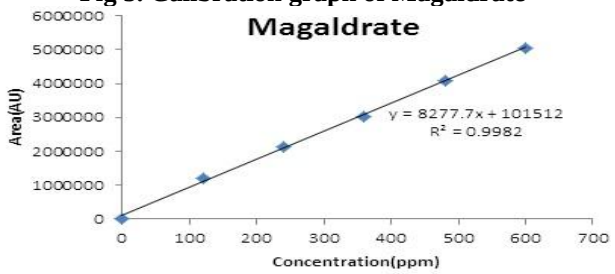


Fig 6. Showing acid degradation

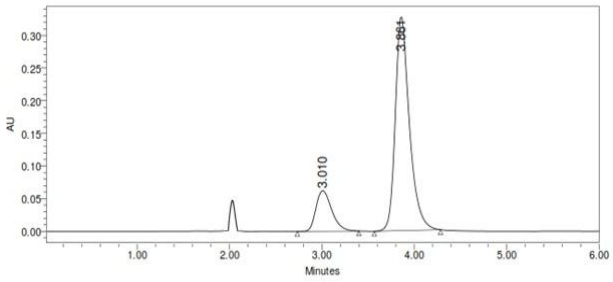


Fig 7. Showing Alkaline degradation

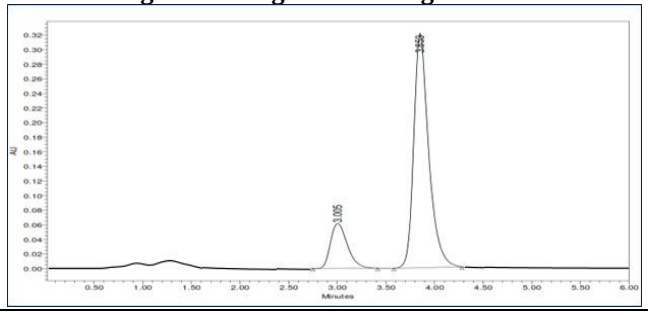


Fig 8. Showing Thermal degradation

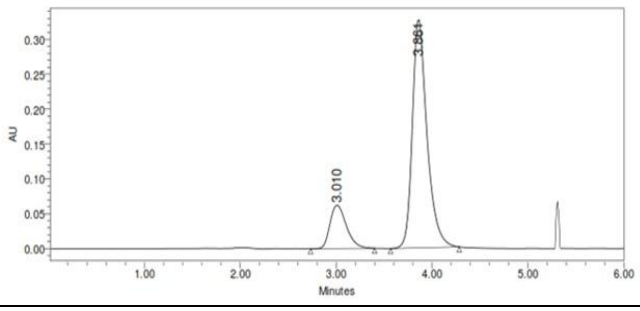


Fig 9. Showing peroxide degradation

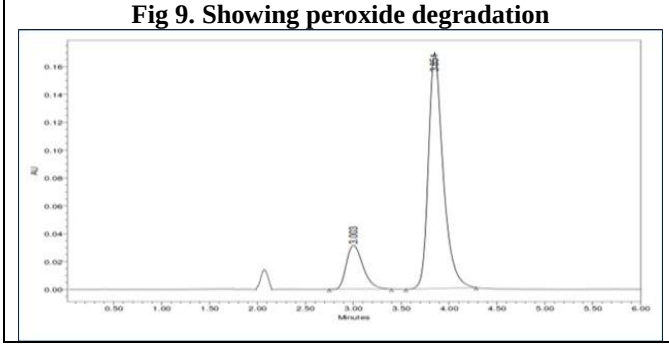
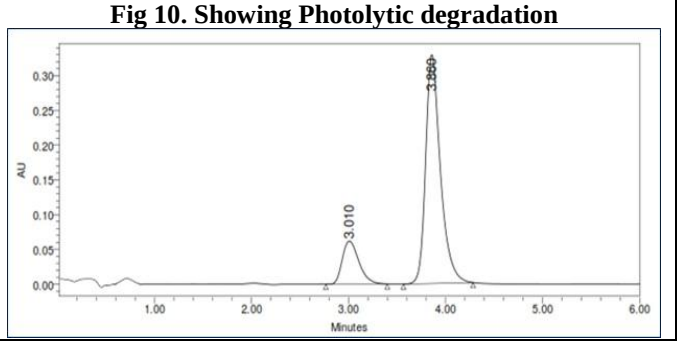


Fig 10. Showing Photolytic degradation



SUMMARY AND CONCLUSION

The analytical method was developed by studying different parameters. First of all, maximum absorbance was found to be at 220nm and the peak purity was excellent. Injection volume was selected to be 10µl which gave a good peak area. The column used for study was Sunfire C18 (4.6×250mm) 5µ because it was giving good peak. 35 º C temperatures was found to be suitable for the nature of drug solution. The flow rate was fixed at 0.9ml/min because of good peak area and satisfactory retention time. Mobile phase is Water and Acetonitrile (60:40% v/v) was fixed due to good symmetrical peak. So this mobile phase was used for the proposed study. Run time was selected to be 6min because analyze gave peak around 3.0, 3.8 ±0.02min of Simethicone and Magaldrate respectively and also to reduce the total run time. The percent recovery was found to be 98.0-102 was linear and precise over the same range. Both system and method precision was found to be accurate and well within range. The analytical method was found linearity over the range 5-25µg/ml of Simethicone and 120-600 µg/ml of Magaldrate of the target concentration. The analytical passed both robustness and ruggedness tests. On both cases, relative standard deviation was well satisfactory.

CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of Magaldrate and Simethicone in bulk drug and pharmaceutical dosage forms. This method was simple, since diluted samples are directly used without any preliminary chemical derivatisation or purification steps. Magaldrate and Simethicone was freely soluble in ethanol, methanol and sparingly soluble in water. Water and Acetonitrile (60:40% v/v) was chosen as the mobile phase. The solvent system used in this method was economical. The %RSD values were within 2 and the method was found to be precise. The results expressed in Tables for RP-HPLC method was promising. The RP-HPLC method is more sensitive, accurate and precise compared to the Spectrophotometric methods. This method can be used for the routine determination of Magaldrate and Simethicone in bulk drug and in Pharmaceutical dosage forms.

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CONFLICT OF INTEREST

No interest

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