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Stability Indicating Simultaneous Equation Method for Determination of Domperidone and (S)-Esomeprazole Magnesium in Capsule Dosage Form Using UV-Spectrophotometer

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Authors' contributions

This work was carried out in collaboration between all authors. Author SS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors JR, I and NC managed the analyses of the study. Author SS managed the literature searches. Authors HG, AKY, VKA and SC help for arrangement of APIs. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Stability indicating simultaneous equation method for determination of Domperidone and Esomeprazole Magnesium in capsule dosage form using UV-Spectrophotometry.
Study Design: A new simultaneous equation method was developed and validated for the determination of esomeprazole magnesium and domperidone in capsule dosage form.

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Place and Duration of Study: Department of Pharmaceutical Chemistry, Invertis Institute of Pharmacy, Invertis University, Bareilly, Uttar Pradesh during July 2012 to June 2013.
Methodology: Simultaneous equation method was performed for estimation of dosage form and degradants.
Results: The maximum wavelength (λ_{max}) was found to be 299 nm for esomeprazole magnesium and 287 nm for domperidone. The linearity range was found to be *1-6* µg ml^{-1} (r^2= *0.998*) and *5-30* µg ml^{-1} (r^2= *0.999*) for esomeprazole magnesium and domperidone, respectively. The value of limit of detection and limit of quantification was *0.116* and *0.386* µgml^{-1} for esomeprazole magnesium and *0.657* and *2.18* µgml^{-1} for domperidone, respectively. Forced degradations were carried out under acid, base, thermal, photolytic and oxidative stress conditions. The method was satisfactorily validated as per the ICH guideline.
Conclusion: This study shows that the proposed spectrophotometric method is useful for the routine determination of esomeprazole magnesium and domperidone in its combined pharmaceutical dosage form.

Keywords: Esomeprazole magnesium; domperidone; simultaneous equation; forced degradation studies; validation.

1. INTRODUCTION

(S)-Esomeprazole Magnesium (EOZ) (Fig. 1) is chemically bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2pyridinyl)methyl]sulfinyl]-1-H-enzimidazole-1-yl), a compound that inhibits gastric acid secretion [1,2]. (S)-Esomeprazole Magnesium is cost effective in the treatment of gastric oesophageal reflux diseases. It is S-isomer of omeprazole and is the first single optical isomer proton pump inhibitor. It provides better acid control than current racemic proton pump inhibitors and has a favourable pharmacokinetic profile relative to omeprazole. Domperidone (DOMPE) (Fig. 1), a dopamine antagonist is usually given along with proton pump inhibitors as ulcers are usually attended with vomiting. Chemically, it is [5-chloro-1-[1,3-(2,3-dihydro-2-oxo-1*H*-benzmidazole-1yl)propyl)-4-piperdinyl-1,3-dihydro-2*H*-benzimidazole-2-one] [3,4]. The stability-indicating assay is a method that is employed for the analysis of stability samples in pharmaceutical industry [5,6,7]. Stability testing plays an important role in the process of drug development. The purpose of stability testing is to provide confirmation on how quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and enables recommendation of storage conditions, and shelf life to be established [8]. The method is expected to allow analysis of individual degradation products [9].

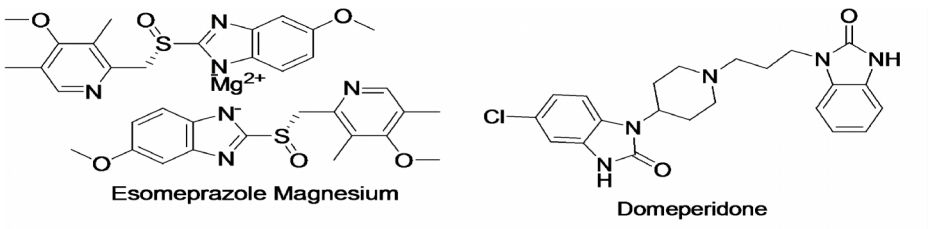

Fig. 1. Chemical structure of esomeprazole and domperidone

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Esomeprazole magnesium was received as gift sample from Metrochem API pvt. Ltd., Hyderabad and domperidone maleate was received as gift sample from Sidmech Laboratories India pvt. Ltd., Dehradun. Methanol was used of analytical grade. All other reagents used were of analytical grade for the forced degradation studies. The pharmaceutical dosage form used in this study was Esofag-D labelled to contain 40 mg of esomeprazole and 30 mg of domperidone per capsule were purchased from local market.

2.2 Apparatus

A UV-Visible spectrophotometer, model UV-3200 (Labindia) with 1cm quartz cells. An electronic balance (Roy electronics- LCBCN5) was used for weighing the samples. Hot Air Oven (Coslab CLE-101) was used for the thermal degradation study. A Sonicator (Labfit) was also used.

2.3 Standard Stock Solution

Standard stock solution (1000 µg/ml) of esomeprazole and domperidone were prepared by dissolving accurately about 50 mg of each drug separately in methanol in 50 ml volumetric flask. The working solution was in the range of 1-6 µg/ ml for esomeprazole and 5-30 µg/ ml for domperidone were prepared by further dilution for calibration curves.

2.4 Method Development

2.4.1 Simultaneous equation method

Zero order overlain spectra (Fig. 2) were carried out at 299 nm and 287 nm, the maximum absorbance wavelength of esomeprazole magnesium and domperidone respectively. Appropriate dilution were prepared using methanol from the stock solution 1000 µg/ ml of esomeprazole magnesium and domperidone to get aliquots of the concentration of 1-6 µg/ ml and 30 µg/ ml for esomeprazole and domperidone respectively. The calibration curve (Fig. 3) was plotted from mean absorbance values of observation of the six replicate. The absorptivity values for both the drug were determined at their respective λmax by measuring absorbance values for working standard of esomeprazole magnesium and domperidone. The concentration of esomeprazole magnesium and domperidone were determined by solving the following equation [10].

$$C_{X=} (A_1a_{y2}-A_2a_{y1}) / (a_{x1}a_{y2}-a_{x2}a_{y1}) \quad (1)$$

$$C_Y = (a_{x1}A_2-a_{x2}A_1) / (a_{x1}a_{y2}-a_{x2}a_{y1}) \quad (2)$$

Where C_x and C_y are the concentration of esomeprazole and domperidone respectively.

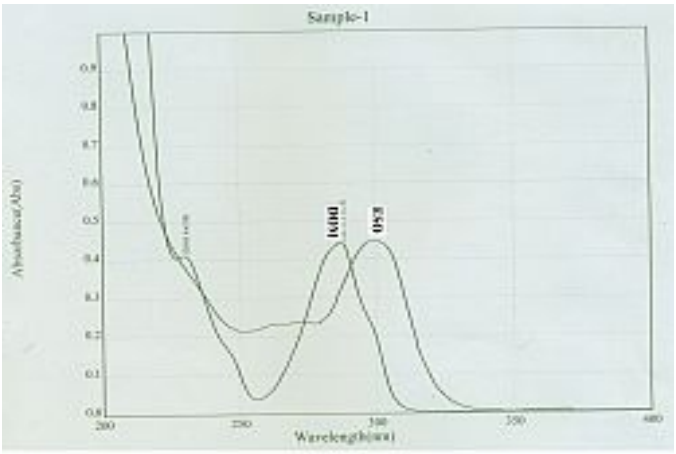

Fig. 2. Overlain spectra of esomeprazole (299 nm) and domperidone (287 nm)

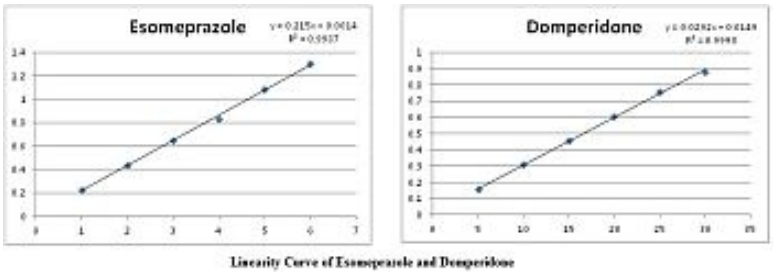

Fig. 3. Linearity curve of esomeprazole and domperidone

2.4.2 Analysis of commercial formulation

Twenty capsules were accurately weighed and its contents crushed to fine powder. Powder equivalent to 40 mg of esomeprazole and 30 mg of domperidone was weighed and dissolved in methanol, sonicated for 10 minute and filtered through Whatman's filter paper no. 41. After rejecting first few ml, different concentrations of capsule sample were prepared by serial dilution technique and analyzed at 299 and 287 nm wavelength.

2.4.3 Recovery studies

To study the accuracy of the proposed methods, recovery studies were carried out by standard addition method at three different levels (80%, 100% and 120% of the test concentration as per ICH guidelines). A known amount of drug was added to pre analyzed capsule powder and percentage recoveries were calculated. The result of recovery studies was satisfactory.

2.4.4 Linearity and range

The six point calibration curve that were constructed were linear over the concentration range between 1-6 µg/ml for esomeprazole and 5-30 µg/ml for domperidone respectively. Each concentration was repeated for 3 times.

2.4.5 Precision

For evaluation of intraday precision repeatability of the result was evaluated for the concentration of 1 µg/ml for esomeprazole and 15 µg/ml for domperidone by 3 replicate determination at interval of 1 hour and for evaluation of interday precision repeatability of the result was evaluated for the concentration of 1 µg/ml for esomeprazole and 15 µg/ml for domperidone by 3 replicate determination at interval of 1 hour for 3 days.

2.4.6 Limit of detection

Limit of detection for esomeprazole was found to be 0.116 and for domperidone was found to be 0.657.

2.4.7 Limit of quantification

Limit of quantification for esomeprazole and domperidone was found to de 0.386 and 2.18 respectively.

2.4.8 Robustness

Robustness of proposed method was performed by changing the UV analyst and remaining condition was keeping constant.

2.5 Stability Indicating Assay Method

2.5.1 Acid degradation

In the 1 µg/ml solution of esomeprazole magnesium and 15 µg/ml solution of domperidone 10 ml 1N HCl were added and kept at room temperature for 24 hours.

2.5.2 Base degradation

In the 1µg/ml solution of esomeprazole magnesium and 15µg/ml solution of domperidone 10 ml 1N NaOH were added and kept at room temperature for 24 hours.

2.5.3 Thermal degradation

About 50 mg of drug substance kept at 60ºC for 8 hours. Then the solution was prepared to achieve 1µg/ml for esomeprazole magnesium and 15 µg/ml for domperidone respectively.

2.5.4 Photolytic degradation

About 50 mg of drug substance kept direct to the sun light for 12 hours. Then the solution was prepared to achieve 1µg/ml for esomeprazole magnesium and 15 µg/ml for domperidone respectively.

2.6 Statistical Analyses

Means, standard deviation (SD), relative standard deviation (RSD) and linear regression analysis were calculated using Microsoft Excel 2007.

3. RESULT AND DISCUSSION

Many pharmaceutical compounds undergo degradation during storage or even during the different processes of their manufacture. Several chemical or physical factors can lead to the degradation of drugs [11]. Hydrolysis and oxidation are the most famous chemical degradation routes of drugs [12,13]. The main classes of drugs that are subject to degradation are esters, amides and lactams. Ester hydrolysis is frequently base catalysed, which makes the reaction rapid, and irreversible [14].

In UV- Spectroscopic method, the crossing points of spectra were utilized for developing the equation for simultaneous analysis and analytical data are present in Table 1.

Table 1. Analysis of commercial formulation in capsule dosage form

Formulation	Drug	Label claim (mg)	% Label claim (Mean± SD)
Capsule	Esomeprazole magnesium	40 mg	92± 0.01845
	Domperidone	30 mg	98± 0.000573

In the method, wavelengths were utilized 299 nm for esomeprazole magnesium and 287 nm for domperidone. The percentage recovery value obtained was within standard limit of 98% to101% for the method which confirmed that the method was accurate and free from any interference of excipients. The low value of standard deviation obtained confirmed precision of the method. The reproducibility, repeatability and accuracy of the proposed method were found to be satisfactory, limit of detection and limit of quantitation was calculated, the result was satisfactory. All recovery studies were compiled in Table 2.

Table 2. Validation parameters for UV-Spectroscopic methods

Validation parameter	Mean±SD	
	Esomeprazole magnesium	Domperidone
Linearity range	1-6µg/ ml	5-30 µg/ ml
Correlation coefficient	0.998	0.999
Slope	0.215	0.0292
Intercept	0.0014	0.0149
Precision		
Interday		
1st day	42.3± 0.000183	106± 0.000566
2nd day	48.4± 0.000253	94± 0.000404
3rd day	40.9± 0.00019	100.7± 0.000499
Intraday		
(1st hrs)	39.3± 0.000129	94± 0.000927
(2nd hrs)	39.4± 0.000294	94± 0.000432
(3rd hrs)	48.3± 0.000126	94± 0.00034
Recovery		
80%	101±0.0024	98±0.0059
100%	55±0.00096	96±0.00033
120%	49±0.0011	99±0.00091
LOD (mg/ml)	0.116 mg/ml	0.657 mg/ml
LOQ (mg/ml)	0.386 mg/ml	2.18 mg/ml
Robustness	107± 0.000974	91± 0.000125

Acedic degradation, alkali degradation, thermal degradation and photolytic degradation was performed successfully by ICH guideline Q1A(R2), result is summerized in Table 3.

Table 3. Forced degradation studies

Condition	Absorbances (λ)		Mean ± SD*		Result (% degradation)	
	ESO	DOM	ESO	DOM	ESO	DOM
Acid degradation	No abs.	No abs.	-	-	-	-
Alkaline degradation	298nm	298 nm	3.1295± 0.0276	0.1640± 0.0103	100%	36.06%
Thermal degradation	288 nm	287 nm	0.2606± 0.00012	1.3786± 0.00082	101%	100%
Photolytic degradation	299 nm	287 nm	0.1407± 0.00507	0.0524± 0.00017	62.9%	11.5%

Degradation study was conducted for domperidone and esomeprazole magnesium in acidic medium. It was found that the drug does not produce any degradates Fig. 4.

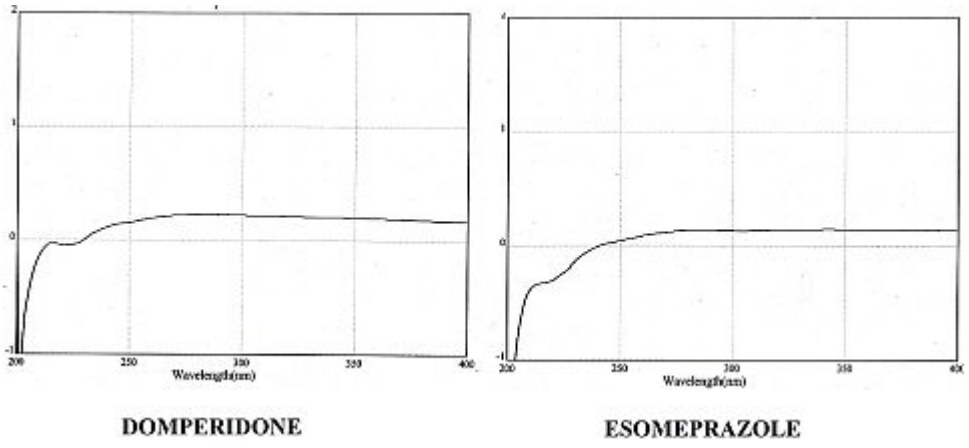

Fig. 4. Acidic degradation of esomeprazole and domperidone

Domperidone and esomeprazole magnesium when hydrolysed with alkali, produced their degradation product. Domperidone showed the parent peak at 220 and 217 nm and esomeprazole magnesium showed numerous peaks starting from 319 to 206 nm Fig. 5.

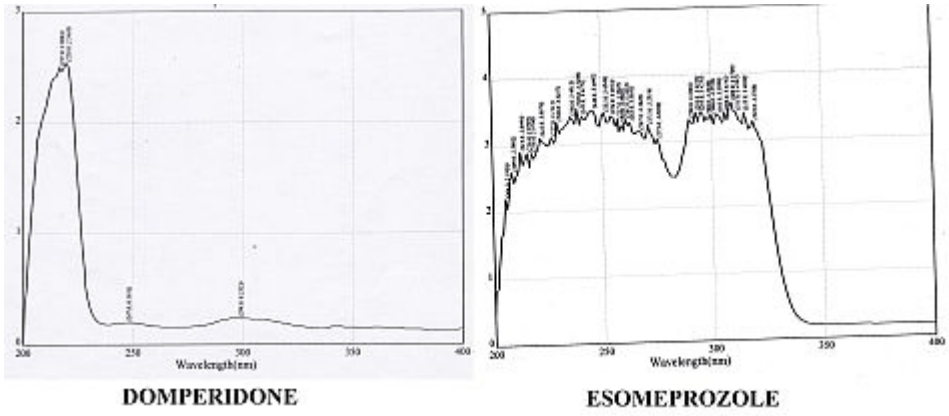

Fig. 5. Basic degradation of esomeprazole and domperidone

Fig. 6 shows thermal degradation of domperidone and esomeprazole magnesium which informs the formation of degradants and the parent peak was observed at 287 and 230 nm for domperidone and 288 nm for esomeprazole magnesium.

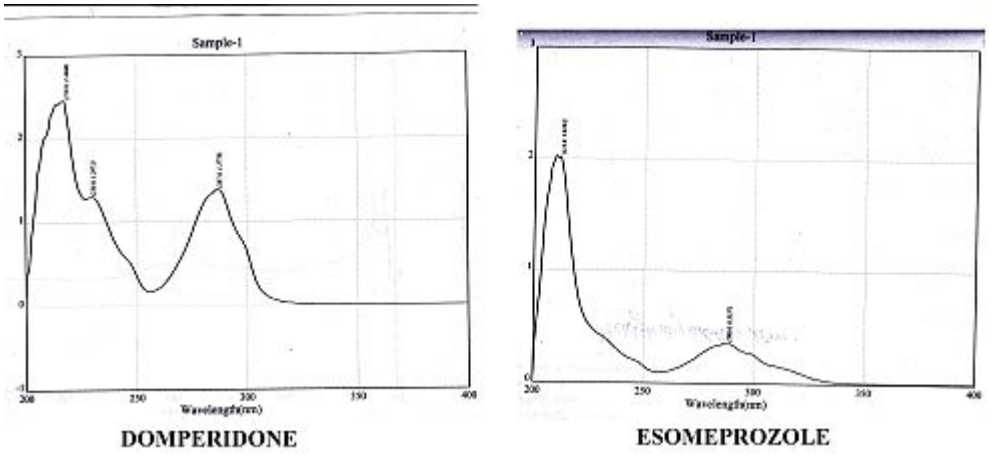

Fig. 6. Thermal degradation of esomeprazole and domperidone

Photolytic degradation was performed in combination, the drugs produced degradates and showed the parent peak at 287, 231, 210 nm for domperidone and 299, 209, 204 nm for esomeprazole magnesium. Fig. 7

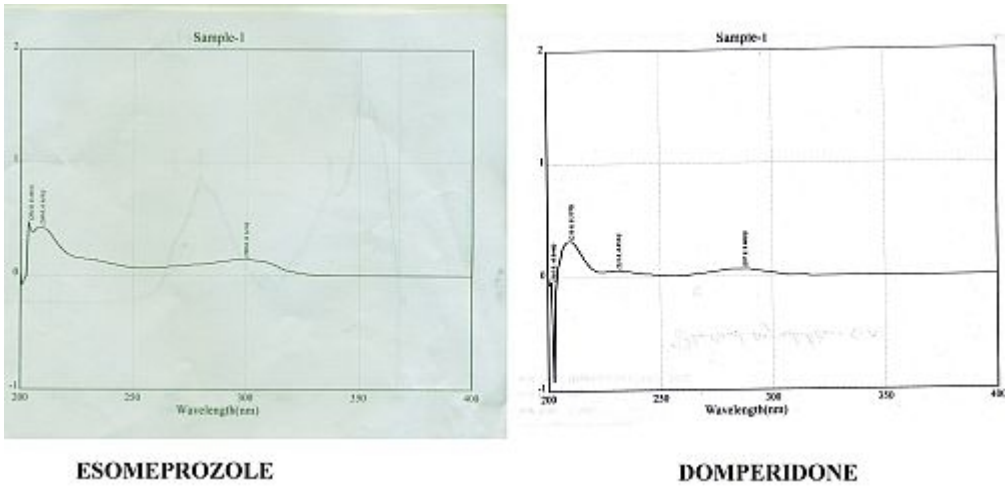

Fig. 7. Photolytic degradation of esomeprazole and domperidone

4. CONCLUSION

All these factors lead to the conclusion that the stability indicating simultaneous equation method development is accurate, precise, simple, sensitive and rapid and can be applied successfully for the estimation of esomeprazole and domperidone in bulk and in pharmaceutical formulations without interference. The relative standard deviation (RSD) for all parameters was found to be less than one, which indicate that the validity of method are also within the limit so the proposed method can be used for routine quantative simultaneous estimation of both the drug.

CONSENT

The wark is totally based on the analysis, so this section is not applicable in this paper.

ETHICAL APPROVAL

Ethical Approval Section dose not required so for this article section is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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