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Research Article

DEVELOPMENT AND VALIDATION OF STABILITY INDICATING ASSAY METHOD FOR SIMULTANEOUS ESTIMATION OF ILAPRAZOLE AND DOMPERIDONE IN BULK AND SOLID DOSAGE FORM BY UV-SPECTROSCOPY

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ABSTRACT

A Simple, rapid, precise and accurate stability indicating UV-Spectrophotometric method was developed for simultaneous estimation of Ilaprazole (ILA) and Domperidone (DOM) in bulk and capsule formulation and validated as per ICH guidelines. The solvent used for this method was methanol. The λmax of ILA and DOM were found to be 306 and 288 nm respectively. The linearity for ILA and DOM was in the range of 1-6 µg/ml and 3-18 µg/ml, respectively with regression coefficient(r^2) of 0.999 for both drugs. The % recovery was found to be in the range of 99.29-100.87% and 99.92-100.16% for ILA and DOM respectively. Percentage RSD for precision and accuracy of the method was found to be less than 2% .LOD values for ILA and DOM were found to be 0.0866 µg/ml and 0.4026 µg/ml respectively. LOQ values for ILA and DOM were found to be 0.2625 µg/ml and 1.241 µg/ml respectively. The Forced degradation study is validated as per ICH guidelines. The developed method is suitable for the analysis of tablet formulation for quality control purposes.

Keywords: Ilaprazole, Domperidone, Simultaneous Equation Method, UV Spectrophotometry, Forced degradation study.

INTRODUCTION

Ilaprazole is chemically 2-[4-methoxypropoxy]-3-methyl-2-pyridinyl] methyl] sulfinil] 6-(1H-pyrrol-1—yl)-1H-benzimidazole. Ilaprazole is a new proton pump inhibitor that suppress gastric acid secretion by specific inhibition of the enzyme system of Hydrogen/Potassium adenosine triphosphate(H^+K^+ATPase) at the secretory surface of the gastric parietal cell and is used in the treatment of various gastric disorders such as, gastric and duodenal ulcers, gastro esophageal reflux disease and in pathological hyper secretory conditions.

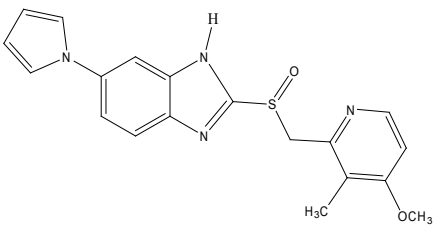

Figure 1: Structure of ILA

Molecular basis of ilaprazole reveals that it is a complex for the estimation by UV method and the methoxy, Benzimidazole and pyridine are the responsible for its therapeutic activity and quality control parameters [1].

Domperidone is Chemically5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl) Propyl]-piperidine-4-yl]-1,3-dihydro-2H-benzimidazol-2-one. Domperidone acts as a gastrointestinal emptying (delayed adjunt and peristaltic stimulant). The gastroprokinetic property of domperidone is related to its peripheral dopamine receptor blocking properties [2].

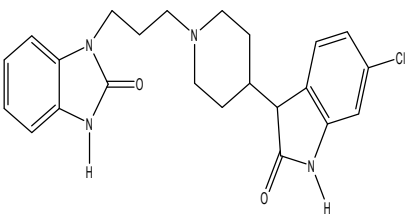

Figure 2: Structure of DOM

A literature survey regarding quantitative analysis of these drugs revealed that there are various analytical methods are described for determination of ILA by UV spectrophotometry[1,3,4] HPLC[5]and DOM by UV[6-8] RP-HPLC[2,9-14]HPLC[15] FT-IR[16] have been reported alone or in combination with other drugs. Till Today there is no stability indicating assay method developed for simultaneous estimation of ILA and DOM in solid dosage form (capsule). The objective of present work was to develop simple, rapid, economic, accurate and precise analytical method for simultaneous estimation of Ilaprazole and Domperidone in bulk and solid dosage form (capsule). The developed method was validated in accordance with ICH guidelines and successfully employed for the assay of ILA and DOM in combined dosage form (capsule).

Stability indicating assay methods

Investigation of stability of drug and its formulation demands such an analytical method which would be capable of selective determination of intact drug, free of interference from its degradation products and other impurities. Such methods are referred as Stability Indicating Assay Methods (SIAM).

Stress testing is carried out under the exposure of variety of severe conditions, such as temperature, humidity, light, acidity, basicity, oxidization and metal catalysis etc. Stress testing is an integral part of every drug regulatory authority guidelines. ICH guideline Q1A (R2) states that the stress testing should be carried out in more extreme conditions of temperature and humidity than that in accelerated stability testing as well as other stresses; from this degradation products and degradation pathways can be established.

MATERIALS AND METHODS

Chemicals and reagents

All the chemicals and reagents used were AR grade. Ilaprazole and Domperidone were obtained as gift samples from Lupin Pharmaceuticals, Mumbai and Wockhardt Pharmaceuticals, Aurangabad respectively. The combined dosage form(Capsule)was purchased from local market.

Instruments

A UV-Visible Spectrophotometer: Shimadzu, Model: UV-1800 with 1 cm matched quartz cell and UV probe 2.33Software was used. Calibrated analytical balance Anamed was used for weighing purpose. Digital Ultrasonic Cleaner (Sonicator): HMG India and Vaccum pump Assembly: Millipore, HPLC grade water system: Millipore. Digital pH Meter: Systronic was used for experimental work.

METHOD DEVELOPMENT

Preparation of standard stock solutions

Accurately weighed 10mg of ILA and 10mg of DOM were transferred into two separate 50ml volumetric flask, dissolved and volume was made up to mark with methanol and sonicated for 20min to give solutions containing 100µg/ml of both ILA and DOM respectively. The stock solutions of both the drugs were further diluted separately with solvent to obtain 10µg/ml solution each and scanned in spectrum mode from 200-400nm.

Selection of analytical wavelength

The solution of concentration 10µg /ml of each drug was prepared and then sample solutions scanned over wavelength range of 200 nm to 400 nm. λmax for ILA and DOM were found at 306 and 288 nm. Representative absorption spectra of ILA and DOM are shown in Figure 3 and 4.

Preparation of calibration curve of ILA and DOM

By appropriate dilution of standard stock solution, different dilutions were prepared ranging from1µg/ml to 6 µg/ml for ILA and 3 µg/ml to 18 µg/ml for DOM. Absorbance of all the dilutions were plotted against the respective concentrations to obtain the calibration curve is shown in Figure 6 and 7.

Analysis of marketed capsule formulation

As per label claim capsule contain 10 mg ILA and 30 mg DOM, So weigh the 10 capsules one by one then calculate the average weight of one capsule then weigh accurately the average weight of one capsule and transferred into 100 ml volumetric flask and dissolved in methanol solution, sonicated for 10 min and filtered. Then different concentrations of capsule sample was prepared by serial dilution method and used for analysis. Prepared capsule sample was analysed on UV spectrophotometer using Simultaneous Equation Method. The analysis procedure was repeated six times with capsule formulation.

$$C_x = (A_2\, ay_1 - A_1\, ay_2)/(ax_2\, ay_1 - ax_1\, ay_2)$$
$$C_y = (A_1\, ay_1 - A_2\, ay_2)/(ax_2\, ay_1 - ax_1\, ay_2)$$

Where, C_x and C_y are the concentrations of ILA and DOM in sample solutions. A_1 and A_2 are the absorbance of sample at 306 and 288 nm.ax_1 and ax_2, ay_1 and ay_2 are the absorptivity of ILA and DOM.

METHOD VALIDATION

The method validation parameters linearity, precision, accuracy, repeatability, limit of detection, limit of quantitation was checked as per ICH guidelines.

Linearity

From the calibration plot of ILA and DOM at their respective absorption maximas, the linearity was observed in the concentration range of 1-6 µg/ml for ILA and 3-18 µg/ml for DOM. Coefficient of correlation (r^2) was found to be 0.9999 for ILA and 0.9999 for DOM. The high value of Coefficient of correlation (r^2) also indicates good linearity of calibration curve for the drugs as shown in Figure 6 and 7.

Accuracy (Recovery Study)

To check the accuracy of proposed method, recovery studies were carried out at 80%, 100%, and 120% of the test concentrations as per ICH guidelines.

To perform recovery study at 100%, 0.387 mg average weight of capsule was weighed and transferred in 100 ml volumetric flask and to this standard 10 mg ILA and 30 mg DOM were added. The volume was made up to the mark with methanol solution and further dilution with same solvent to obtain sample solution Similarly, for 80% recovery study, 8 mg ILA and 24 mg DOM were added, and for 120% recovery study, 12 mg ILA and 36 mg DOM were added respectively. Results of which are given in Table 3.

Precision

Precision studies were carried out to study the Intra-day and Inter-day variations of the response. Intraday precision (% RSD) was assessed by analyzing standard drug solutions within the calibration range, three times on same day. Inter-day precision (%RSD) was assessed by analyzing drug solutions within the calibration range on three different days. The intra-day and inter-day precisions were determined, results of which are given in Table 4 and 5.

Limit of Detection and Limit of Quantitation

LOD and LOQ of the drug were calculated as per ICH guidelines, using following formula.

$LOD = 3.3\times\sigma/S$ and $LOQ = 10\times\sigma/S$

Where, σ = the standard deviation of the response and S= the slope of the calibration curve.

LOD Values for ILA and DOM were found to be 0.0866 µg/ml and 0.4096 µg/ml, respectively. LOQ Values for ILA and DOM were found to be 0.2625 µg/ml and 1.241 µg/ml, respectively.

Table 1: Linear regression data for calibration curve of ILA and DOM

Name of the drug	Linearity range µg/ml	r^2	Slope	Intercept
ILA	1 – 6	0.999	0.059	0.001
DOM	3 – 18	0.999	0.028	0.001

Table 2: Analysis of capsule formulation

Sr. No.	Label claim (mg)		Amount found (mg)		% of Label claim	
	ILA	DOM	ILA	DOM	ILA	DOM
1	10	30	10.14	30.27	100.69	99.90
2	10	30	10.07	30.35	100.00	100.16
3	10	30	10.13	30.31	100.59	100.03
4	10	30	10.00	30.28	99.30	99.93
5	10	30	10.08	30.25	100.09	99.83
6	10	30	10.03	30.29	99.60	99.96
				Mean*	99.95	100.00
				S.D	0.6623	0.0962
				R.S.D	0.6626	0.0962

* Indicates average of six determinations

Table 3: Accuracy (Recovery study data)

Level of Recovery	% Mean recovery		S.D.*		% R.S.D.*	
	ILA	DOM	ILA	DOM	ILA	DOM
80%	100.00	99.99	1.1331	0.0750	1.1331	0.07505
100%	99.999	99.99	1.0650	0.0692	1.0651	0.0693
120%	100.29	100.03	1.3387	0.1410	1.3348	0.1409

* Indicates average of three determinations at each level.

Table 4: Intraday precision data

Sr. No.	Interval of Time	Concentration (µg/ml)		% Recovery	
		ILA	DOM	ILA	DOM
I	Intra-day	5	15	102.58	100.01
II		5	15	99.99	100.00
III		5	15	100.01	100.00
			Mean*	100.86	100.00
			S.D	1.4895	0.0057
			R.S.D	1.4767	0.0057

* Indicates average of three determinations.

Table 5: Inter-day precision data

Sr. No.	Interval of Time	Concentration (µg/ml)		% Recovery	
		ILA	DOM	ILA	DOM
I	Day 1	5	15	100.02	100.02
II	Day 2	5	15	99.99	100.01
III	Day 3	5	15	99.99	100.00
			Mean*	100.00	100.01
			S.D.	0.01732	0.0100
			R.S.D.	0.01732	0.009

* Indicates average of three determination

Table 6: Limit of detection (LOD) and Limit of quantitation (LOQ)

Name of the drug	LOD µg/ml	LOQ µg/ml
ILA	0.0866	0.2625
DOM	0.4096	1.241

Table 7: Forced degradation study

Sr. no.	Stress Condition	% Degradation		% Assay	
		ILA	DOM	ILA	DOM
1	**Acid hydrolysis** (0.1 N Hcl, Reflux at 60ºCfor 4h)	11.13	19.65	88.87	80.35
2	**Alkali hydrolysis** (0.1M NaOH, Reflux at 60ºCfor 4h)	19.59	17.71	80.41	82.29
3	**Neutral hydrolysis** (H_2O, Reflux at 60ºCfor 4h)	15.77	8.76	84.23	91.24
4	**Oxidative degradation** (3% H_2O_2,Reflux at 60°C for 4h)	18.72	8.67	81.28	91.33
5	**Photolytic degradation** (UV Radiation,4h)	13.97	14.70	86.03	85.30
6	**Thermal degradation** (80°C,2h)	10.22	12.92	89.78	87.08
7	**Sunlight degradation** (Keep under sunlight, 4h)	14.14	13.26	85.86	86.74

Table 8: Summary of validation parameters

Parameters		ILA	DOM
Linearity range (µg/ml)		1-6	3-18
Detection Wavelength (nm)		306	288
Correlation coefficient (r^2)		0.999	0.999
Precision (%RSD)	**Intra-day**	1.4767	0.05774
	Inter-day	0.01732	0.009
Accuracy (%)	**80% ± %RSD**	100.00±1.1331	99.99±0.07505
	100% ± %RSD	99.99±1.0651	99.99±0.0693
	120% ± %RSD	100.29±1.3348	100.03±0.1409
Repeatability(%RSD)		0.6791	0.5828
LOD (µg/ml)		0.0866	0.4096
LOQ (µg/ml)		0.2625	1.241

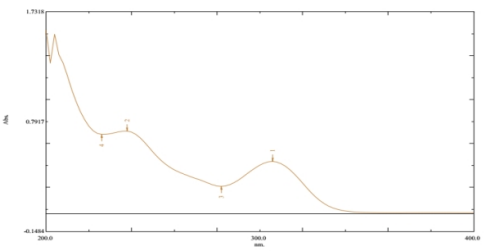

Figure 3: Absorption spectra of ILA

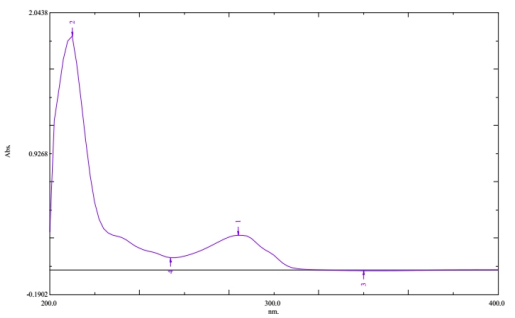

Figure 4: Absorption spectra of DOM

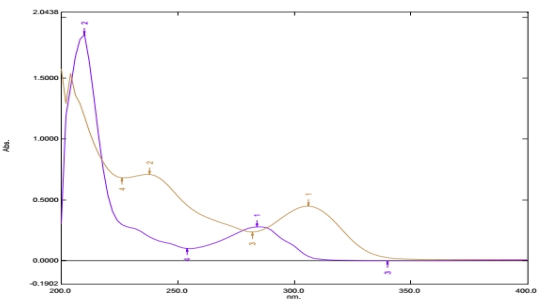

Figure 5: Overlay spectra of both ILA and DOM

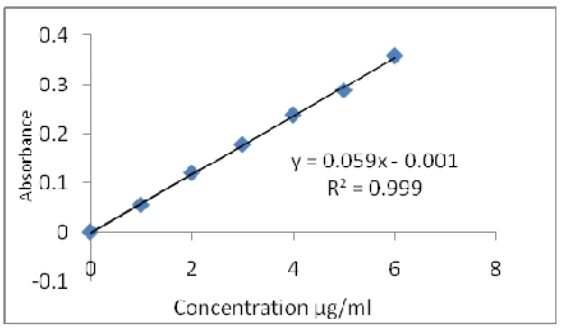

Figure 6: Calibration Curve of ILA

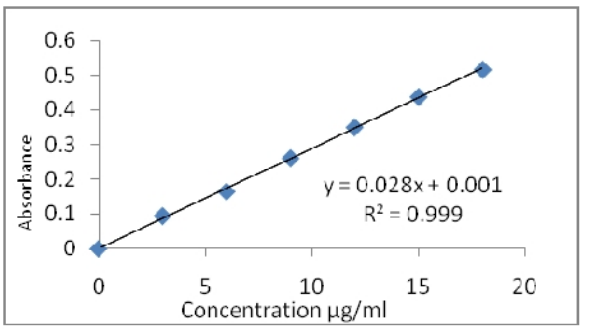

Figure 7: Calibration Curve of DOM

RESULTS AND DISSCUSSION

In the present work, new stability indicating simultaneous estimation method was developed for the simultaneous spectrophotometric estimation of ILA and DOM in commercially available capsule dosage form. The method utilizes easily available and cheap solvent for analysis of ILA and DOM in capsule dosage form. The common excipients and other additives are usually present in capsule dosage form do not interfere in the analysis of ILA and DOM in method, Hence it can be conveniently adopted for routine quality control analysis of the drugs in combined pharmaceutical formulation. The relative standard deviation were found to be within the limit, indicating good accuracy, precision, and repeatability of the proposed method.

CONCLUSION

A simple, Sensitive, accurate and precise stability indicating UV Spectrophotometric method has been developed for quantitative determination of Ilaprazole and Domperidone in bulk and solid dosage form(Capsule). The UV spectrum was scanned between 200 to 400nm range and 306 nm for ILA and 288 nm for DOM was selected as maximum wavelength for absorption. Beer's law was obeyed in the concentration range 1-6µg/ml for ILA and 3-18µg/ml for DOM. Recovery was calculated, and high percentage of recovery showed that the method is accurate. The method is simple and rapid. Results of the analysis validated as per ICH guidelines. Hence, the method can be used for quality control of finished pharmaceutical dosage form.

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