IAU-ARAK

J. Iran. Chem. Res. 4 (2011) 25-31

Journal of the Iranian Chemical Research

www.iau-jicr.com

Application of hydrotropic solubilization in spectrophotometric analysis of Esomeprazole and Itopride pharmaceutical combined tablet dosage forms

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Received 23 December 2010; received in revised form 23 February 2011; accepted 27 February 2011

Abstract

Two simple, accurate and precise methods for simultaneous estimation of Esomeprazole and Itopride in bulk drug and tablet dosage form have been described. Method-A employs formation and solving of simultaneous equation using 231 and 370 nm as two analytical wavelengths. Method -B is Absorption ratio method, which uses 308 and 331 nm as two analytical wavelengths.Beer's law was obeyed in the concentration range 5-35 µg/ml for Esomeprazole and 5-40 µg mL^{-1} for Itopride. In the present investigation, 0.5 Metformin hydrochloride solutions (hydrotropic solubilizing agent) were employed to solubilize, Esomeprazole and Itopride from fine powder of its tablets to carryout Spectrophotometric analysis. The optimized methods showed good reproducibility and recovery with standard deviation of < 1.0% and percent relative standard deviation less then 2.0%, allow the simultaneous estimation of Esomeprazole and Itopride in concentration ranges employed for this purpose in the assay of bulk drug and tablets.

Keywords: Hydrotropic agent; Esomeprazole; Itopride hydrochloride.

1. Introduction

Hydrotropy is a solubilization process whereby addition of large amount of second solute results in an increase in aqueous solubility of another solute. Various techniques have been employed to enhance the aqueous solubility of poorly water soluble drugs such as alteration in pH of solvent, co-solvents, complexation etc. Hydrotropic Solubilization is one of them. Sodium salicylate sodium acetate, sodium citrate and urea sodium benzoate, niacinamide [1] have been employed as a hydrotropic agent which enhances the aqueous solubility of many poorly water soluble drugs. Esomeprazole magnesium trihydrate [2] (ESO) is chemically bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl - 2 -pyridinyl)methyl]sulfinyl] - 1-H - enzimidazole - 1 -yl) magnesium trihydrate , a compound that inhibits gastric acid secretion . Esomeprazole 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 [3]. Literature survey of revealed the estimation of omeprazole by UV Spectrophotometric method [4, 5], HPLC [6, 7] methods.Itopride hydrochloride is N-[P-[2-

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[dimethylamino] ethoxyl] benzyl] veratramide hydrochloride and has anticholinesterase activity as well as dopamine D_2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders.

A very few reports were found for the analysis in capsule formulations in individual form for rabeprazole sodium and itopride hydrochloride [8, 9]. Author of the article and his research team has developed a UV Method development different pharmaceutical dosage form by hydrotropic agents [10-18]. Method-A is based on simultaneous equation method and method B is based on determination of Q-value. Results of analysis for methods were tested and validated for various parameters according to ICH guidelines, hence can be adopted for the routine analysis of Esomeprazole and Itopride in tablet dosage form. The pH of 0.5 Metformin hydrochloride solutions was 8.5.Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide, and benzene have been employed for the solubilization of poorly water soluble drugs for Spectrophotometric estimations. Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. The proposed method is new, accurate, simple and economic.

2. Experimental

UV-visible double beam spectrophotometer, Shimadzu model 1700 with spectral bandwidth of 1 nm, wavelength accuracy of ± 0.3 nm and a pair of 10 mm matched quartz cells was used. Acetonitrile, Ammonium acetate and Methanol (HPLC grade, S.D. Fine The commercially available tablets, Tablet formulation containing 50 mg of E SO and 50 mg of ITO is available (Lorilip Micro Labs. Ltd., Pondicherry, Tornet-TG Lupin LTD, Mumbai) was procured from local market.

2.1. Preliminary solubility studies of drug and calibration curve

Solubility of both drugs was determined at 25 ± 1 °C. An excess amount of drug was added to three screw capped 70 mL glass vials containing different aqueous system viz. distilled water, buffer of pH 8.5, 0.5 Metformin hydrochloride solutions. The vials were shaken for 15 hrs at 25 ± 1 °C in a mechanical shaker. These solutions were allowed to equilibrate for the next 33 hrs and then centrifuged for 5 minutes at 2100 rpm. The supernatant of each vial was filtered through Whatman filter paper No. 41. The filtrates were diluted suitably and analyzed spectrophotometrically against corresponding solvent blank. The standard stock solutions of Esomeprazole and Itopride were prepared by dissolving 50 mg of each drug in 50 mL of 0.5 Metformin hydrochloride solutions and final volume was adjusted with distilled water in 100ml of volumetric flask. From the above solution 10 mL of solution was taken and diluted to 50 mL with distilled water to get a solution containing 100 µg mL of each drug. Working standard solutions were scanned in the entire UV range of 400-200 nm to determine the λ_{max} of both drugs. The λ_{max} of Esomeprazole and Itopride were found to be 231 nm and 270 nm respectively and from overlain spectra (Fig. 1) it is evident that isobestic point was obtained at 262.1 nm. Eight working standard solutions for both drugs having concentration 5, 10, 15, 20, 25, 30, 35, 40µg/ml were prepared in distilled water from stock solution. The absorbance's of resulting solutions for both drugs were measured at 231, 270 nm for method A, 262.1,270 nm for method and plotted a calibration curve against concentration to get the linearity and regression equation of both drugs. Six mixed standards solutions with concentration of Esomeprazole and Itopride in µg/ml of 30:5,25:10,20:15,15:20,10:25,5:30 were prepared in distilled water by diluting appropriate volumes of the standard stock solutions.

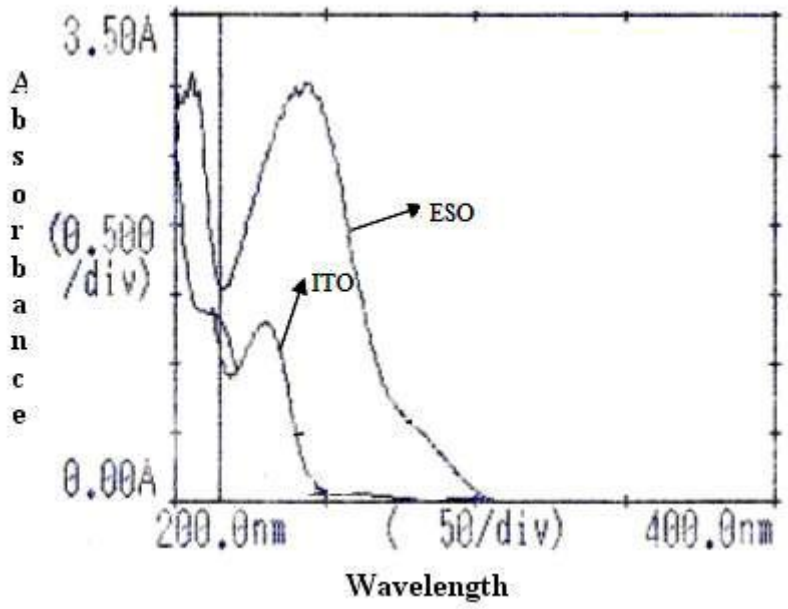

Fig. 1. Overlain spectra of Esomeprazole and Itopride.

2.2. Simultaneous equation method (Method A)

For Selection of analytical wavelength for Simultaneous Equation Method [19-20].The wavelength 231 nm (λ_{max} of ESO) and 270 nm (λ_{max} of ITO) was selected (Fig1). The absorbencies of ESO and ITO were measured at 231 nm and 270 nm. This method of analysis is based on the absorption of drugs X and Y at the wavelength maxima of the other. The quantification analysis of ESO and ITO in a binary mixture were performed by using Eqn-1 and Eqn-2. Where Cx and Cy are the concentrations of ESO and ITO respectively in the diluted sample, ax1 and ax2 are absorptivities of ESO at equation 1 and equation 2 having values 432.1 and 196.6, ay1 and ay2 are absorptivities of ITO at equation 1 and equation 2 having values 239 and 248 nm respectively. A_1 and A_2 are the absorbances of samples at the 229 and 303 respectively.

CX = A2ay1- A1ay2 / ax2ay1- ax1ay2 Eq.1
CY = A1ax2- A2ax1 / ax2ay1-ax1ay2 Eq.2

2.3. Absorbance ratio method (Method B)

In absorption ratio method [19, 20] absorbances of both the drugs were calculated at two selected wavelengths; among which λ_1 is the wavelength of isoabsorptive point of both drugs and λ_2 is the λ max of either drug among both drugs. From the overlain spectra (Fig. 1) wavelength 262.1 nm (isoabsorption point) and 258 nm (λ_{max} of ESO) were selected for study. The absorbencies at 266 nm and 287 nm for ITO were obtained and similarly for ESO absorbencies are measured at 274 nm and 286 nm. The absorptivity values E (1%, 1cm) determined for Esomeprazole at 266 and 287 nm were 278 (ax_2) and 294 (ax_1) while respective values for Itopride were 308 (ay_2) and 331 (ay_1). These values were means of six estimations. The absorbances and absorptivity at these wavelengths were substituted in following equations to obtain the concentration of both drugs.

$$CESO = \frac{Q_M - 1.248}{2.8410} x \frac{A_1}{266.0} \qquad \text{Eq. 3}$$

$$CITO = \frac{Q_M - 0.2971}{-1.0789} x \frac{A_1}{331.0} \quad \text{Eq. 4}$$

where C_{ESO} and C_{ITO} are concentration of Esomeprazole and Itopride respectively in g/100mL. A_1 and A_2 were the absorbance of the sample at 308 nm and 331.0 nm respectively,

2.4. Method validation

2.4.1. Repeatability

To check the degree of repeatability of the methods, suitable statistical evaluation was carried out. Repeatability was performed for six times with tablets formulation. The standard deviation, coefficient of variation and standard error was calculated. The result of statistical evaluation are given in Table 2.

2.4.2. Intermediate Precision- (Inter-day and Intra-day precision)

The inter-day and intra-day precision was determined by assay of the sample solution on the same day and on different days at different time intervals respectively. The results of the same are presented in Table 3.

2.4.3. Linearity

For each drug, appropriate dilutions of standard stock solutions were assayed as per the developed methods. For method-I and II, the Beer- Lambert's concentration range was found to be 5-35 µg mL^{-1} for ESO and 5-40 µg mL^{-1} for ITO. The linearity data for both methods are presented in Table 1.

Table 1
Optical Characteristics data of Esomeprazole and Itopride

Parameters	**Method-A**		**Method-B**	
	ESO	**ITO**	**ESO**	**ITO**
Working λ (nm) in 0.5 Metformin hydrochloride solution	239	244	308	331
Beer's law limit (µg mL^{-1})	5-35	5-35	5-40	5-40
Absorptive E(1%,1cm) *	231	248	318	351
Correlation Coefficient *	0.9998	0.9997	0.9999	0.9998
Intercept *	0.246	0.0041	0.0074	0.0048
Slope *	0.194	0.0417	0.0161	0.0218

ESO- Esomeprazole, ITO: Itopride,
*Average of six estimation

2.4.4. Accuracy

To check the accuracy of the proposed methods, recovery studies were carried out at 80,100, and 120% of the test concentration as per ICH guidelines. The recovery study was performed three times at each level. The results of the recovery studies are given in Table 2.

Table 2
Analysis data of tablet formulation, statistical validation and recovery studies.

Method	Drug	Label claim mg/tab	Amount found* mg/tab	Label claim (%)	S.D.*	COV (%)	S.E.*	Amount added (%)	Recovery (%)
I	ESO	50	50.01	100.01	0.214	0.0325	0.594	80	100.04
								100	99.94
								120	100.11
	ITO	50	49.25	99.86	0.0781	0.197	0.207	80	99.96
								100	90.15
								120	100.20
II	ESO	50	50.11	100.09	0.369	0.328	0.441	80	100.01
								100	99.91
								120	100.0
	ITO	50	50.04	100.04	0.217	0.494	0.180	80	99.89
								100	100.18
								120	100.05

ESO- Esomeprazole, ITO: Itopride,
S.D.: Standard deviation, COV: Coefficient of variation, S.E.: Standard error,
*Average of six estimation of tablet formulation,
Average of three estimation at each level of recovery

2.4.5. Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD & LOQ of Esomeprazole and Itopride by proposed methods were determined using calibration standards. LOD and LOQ were calculated as 2.5 σ/S and 8.5 σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response. The results of the same are shown in Table 3.

Table 3
Validation parameters.

Method	Drug	LOD*	LOQ*	Precision (% COV)			
				Intraday n=6	Inter day *		
					First day	Second day	Third day
I	ESO	0.1642	0.2209	0.8904	0.6509	0.6902	0.6771
	ITO	0.0536	0.2182	0.9063	0.8946	0.7891	0.6812
II	ESO	0.02517	0.5719	0.6781	0.8104	0.7610	0.7701
	ITO	0.1829	0.0832	0.5690	0.4581	0.5615	0.8032

ESO- Esomeprazole, ITO: Itopride,
COV: Coefficient of variation,
* Average of six determination

2.4.6. Analysis of the tablet formulations

Twenty tablets of marketed formulation were accurately weighed and powdered. A quantity of powder equivalent to 50 mg of Esomeprazole and Itopride was transferred to 100 mL volumetric flask and dissolved in 50 mL of 0.5 Metformin hydrochloride with frequent shaking for 15 minutes and final volume was made up with distilled water. The sample solution was then filtered through Whatmann filter paper No. 41 and first few ml were rejected. From the above solution 10 mL of solution was taken and diluted to 50ml with distilled water to get a solution containing 100 µg mL of Esomeprazole and corresponding concentration of Itopride. This solution contains Esomeprazole and Itopride in the proportions of 2:4:7.5.0 ml of solution was transferred in 10ml volumetric flask and diluted with distilled water to obtain final concentration of 10 µg mL^{-1} of Esomeprazole and 20µg mL^{-1} of Itopride. For method-I absorbance of the sample solution viz. A_1 and A_2 were recorded at 239 and 244 nm respectively and concentration of two drugs in the sample were determined using Eqn.1 and 2. For method-II, absorbances of the sample solution viz. A_1 and A_2 were recorded at 262.1 nm (isobestic point) and 308 nm, λ_{max} of Esomeprazole, respectively and ratio of absorbance were calculated viz. A_2/A_1. Concentrations of two drugs in the sample were calculated using eq.3 and 4.

3. Results and Discussions

The primary objective of the present investigation was to employ hydrotropic solutions to extract the drugs from their dosage forms precluding the use of costlier organic solvents. The term hydrotropy has been used to designate the increase in solubility of various substances in water due to the presence of large amounts of additives. Most of the organic solvents like ethanol, methanol, acetonitrile, hexane, cyclohexane, diethyl ether, chloroform and toluene find wide use in Spectrophotometric analysis of poorly water-soluble drugs. Most of these organic solvents are toxic in nature, costlier and responsible for pollution moreover inaccuracy in Spectrophotometric estimation due to volatility is another drawback of organic solvents.

The validity and reliability of proposed methods were assessed by recovery studies. Sample recovery for both the methods is in good agreement with their respective label claims, which suggested non interference of formulation additives and hydrotropic solubilizing agent 0.5 Metformin hydrochloride in estimation. Percentage estimation of both drugs was found in tablet dosage form were 100.15 and 99.42 in method A, 101.01 and 99.97 in method B for Esomeprazole and Itopride respectively with standard deviation <2 (Table 2).

Solubility studies indicated that aqueous solubility of Esomeprazole and Itopride were enhanced more than 35 and 48 folds in 0.5 Metformin hydrochloride solutions as compared to solubility in distilled water and buffer of pH 8.5 respectively. Linearity range for Esomeprazole and Itopride were found to be 5-35 µg mL^{-1} and 5-40 µg mL^{-1} at respective selected wavelengths and coefficient of correlation were found 0.9991, 0.9984, 0.9974 for Esomeprazole at 239, 244, nm and 0.9994, 0.9999,0.9984 for Itopride at 308,331 nm respectively (Table 1). Precision was determined by studying the repeatability and intermediate precision. Repeatability result indicates the precision under the same operating conditions over a short interval time and inter-assay precision. The standard deviation, coefficient of variance and standard error were calculated method A 0.0325, 0.594, 0.197, and 0.207 and method B 0.369, 0.217 for Esomeprazole and Itopride respectively. The results were mentioned in Table 2. Intermediate precision study expresses within laboratory variation in different days. In both intra and inter-day precision study for both the methods % COV were not more than 1.0% indicates good repeatability and intermediate precision (Table 3). Method A, LOD 0.1642, 0.0536, LOQ 0.2209, 0.2182, for method B LOD, LOQ 0.02517, 0.1829 and 0.5719, 0.0832 respectively Esomeprazole and Itopride.

Both drugs showed good regression values at their respective wavelengths and the results of recovery study reveled that any small change in the drug concentration in the solution could be

accurately determined by the proposed methods and low values of LOD and LOQ indicated good sensitivity of proposed methods.

4. Conclusions

Hence proposed methods are new, simple, cost effective, accurate, sensitive, and precise and can be adopted for routine analysis of Esomeprazole and Itopride in tablet dosage form.

Acknowledgements

The authors are thankful to Prof. D.V. Kohli and Dr Hari Singh Gaur University Sagar (M.P.) to given suggestion and facility. We are highly grateful to reviewer to given valuable suggestions suggestion.

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