A NOVEL VALIDATED RP-HPLC METHOD FOR THE DETERMINATION OF ITOPRIDE HYDROCHLORIDE IN BULK AND PHARMACEUTICAL TABLET DOSAGE FORMS

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ABSTRACT

A simple, specific, accurate, rapid, inexpensive isocratic Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative determination of Itopride HCl in pharmaceutical tablet dosage forms. RP-HPLC method was developed by using Welchrom C₁₈ Column (4.6 X 250mm, 5µm), Shimadzu LC-20AT Prominence Liquid Chromatograph. The mobile phase composed of 10mM Phosphate buffer (pH-3.0, adjusted with triethylamine): acetonitrile (50:50v/v). The flow rate was set to 1.0 mL.min⁻¹ with the responses measured at 235nm using Shimadzu SPD-20A Prominence UV-Vis detector. The retention time of Itopride HCl was found to be 2.650 min. Linearity was established for Itopride HCl in the range of 2-10 µg.mL⁻¹ with correlation coefficient 0.9999. The validation of the developed method was carried out for specificity, linearity, precision, accuracy, robustness, limit of detection, limit of quantitation. The developed method can be used for routine quality control analysis of Itopride HCl in pharmaceutical tablet dosage form.

KEY WORDS: Itopride HCl, Isocratic RP-HPLC, UV-Vis detector, Method Validation.

INTRODUCTION

Itopride hydrochloride (N-[4-[2-(dimethylamino)-ethoxy]benzyl]-3, 4-dimethoxybenzamide hydrochloride) ¹⁻³(Figure 1) is a prokinetic benzamide derivative unlike metoclopramide or domperidone. These drugs inhibit dopamine and have gastro kinetic effect⁴. Itopride HCl is prescribed for non ulcer dyspepsia, chronic indigestion and gastro-esophageal reflux disease. Itopride is effective in reducing bloating, abdominal pain and burning sensation and other gastrointestinal disorders⁵. Itopride increases acetylcholine concentration by inhibiting dopamine D₂-receptors and acetyl cholinesterase. Higher acetylcholine increases gastrointestinal peristalsis, increase the lower esophageal sphincter pressure, increases gastric emptying, stimulates gastric motility and improves gastro duodenal co-ordination. Literature survey reveals that for the determination of itopride HCl and its related substances in biological fluids like plasma, blood, urine and pharmaceutical dosage forms by spectrophotometry⁶⁻⁸, High Performance Liquid Chromatography (RP-HPLC) with UV detection⁹, chemiluminescence detection¹⁰, fluorimetric detection¹¹⁻¹³, Photo Diode Array detection¹⁴ and Liquid Chromatography-Mass Spectrometry¹⁵, HPTLC¹⁶. However, very few analytical methods were reported in literature for the determination of itopride HCl in bulk and pharmaceutical dosage forms. The reported HPLC methods so far in the literature are considered to be uneconomical, time consuming and have poor symmetry. In fact there is a need for the development of a novel, simple, rapid, efficient RP-HPLC analytical method with reproducibility for determination of itopride HCl in bulk and pharmaceutical dosage forms. The present study illustrates development and validation of a novel, simple, rapid and efficient RP-HPLC analytical method with reproducibility for determination of itopride HCl in bulk

and pharmaceutical tablet dosage form. The established method was validated with respect to specificity, linearity, precision, accuracy, robustness, LOD and LOQ according to ICH guidelines¹⁷.

MATERIALS AND METHODS

Chemicals and Reagents

The reference sample of Itopride HCl standard was kindly supplied as gift sample by Hetero Drugs Ltd., Hyderabad, Andhra Pradesh, India. All the chemicals were analytical grade. Potassium dihydrogen orthophosphate from Rankem Ltd., Mumbai, India, while acetonitrile (HPLC grade) and triethylamine (HPLC grade) from Merck Pharmaceuticals Private Ltd., Mumbai, India. Ortho phosphoric acid used was of HPLC grade and purchased from Merck Specialties Private Ltd., Mumbai, India. Commercial tablets of Itopride HCl formulation was procured from local market. ITCAN FC-tablets 50 mg are manufactured by Hetero drugs Pvt. Ltd. Hyderabad, A.P., and GEPRIDE-50 tablets are manufactured by Intralabs Pvt. Ltd. Bangalore, Karnataka.

Instruments

Quantitative HPLC was performed on a isocratic high performance liquid chromatograph (Shimadzu LC-20AT Prominence Liquid Chromatograph) with a LC-20AT VP pump, manual injector with loop volume of 20 µL (Rheodyne), programmable variable wavelength Shimadzu SPD-20A Prominence UV-Vis detector and Welchrom C₁₈ Column (4.6 X 250mm, 5µm particle size). The HPLC system was equipped with “Spinchrome” software. In addition an electronic balance (Shimadzu TX223L), digital pH meter (Systronics model 802), a sonicator (spectra lab, model UCB 40), UV-Visible Spectrophotometer (Systronics model-2203) were used in this study.

Chromatographic conditions

Itopride HCl was analyzed by various reversed phase columns like C₈ and C₁₈ columns. Among C₈ and C₁₈ columns, C₁₈ (250mmX4.6mm, 5µm) column was selected. Various combinations of acetonitrile, phosphate buffer and methanol with triethylamine as column modifier were tested. The mixture of 10mM Phosphate buffer (pH adjusted to 3.0 using triethylamine) and Acetonitrile in ratio of 50:50 v/v was selected as mobile phase and UV detection wavelength was 235 nm with a flow rate of 1mL.min⁻¹. Injection volume was 20µL, with ambient temperature, run time was 6 min. and retention time was 2.650 min. The resulting HPLC chromatogram was shown in Figure 3.

Preparation of mobile phase

A 10mM Phosphate buffer was prepared by dissolving 6.056 g of potassium dihydrogen orthophosphate in 445 mL of HPLC grade water. To this 55mL of 0.1M phosphoric acid was added and pH was adjusted to 3.0 with triethylamine. The above prepared buffer and acetonitrile were mixed in the proportion of 50:50 v/v and was filtered through 0.45 µm nylon membrane filter and degassed by sonication.

Preparation of Standard solution

About 100 mg of pure Itopride HCl was accurately weighed and dissolved in 100 mL of mobile phase at to get 1 mg.mL⁻¹ stock solution. Working standard solution of Itopride HCl was prepared with mobile phase. The final volume was made with the mobile phase. The standard solution was filtered through 0.45 µm nylon membrane filter and degassed by sonication.

Preparation of Sample solution

The content of 20 tablets of Itopride HCl (GEPRIDE-50) were accurately weighed and transferred into a mortar and ground to a fine powder. From this, tablet powder which is equivalent to 100 mg of Itopride HCl was taken and the drug was extracted in 100 mL of mobile phase. The resulting solution was filtered using Whatman Grade No.1 filter paper and degassed by sonication. This solution was further suitably diluted for chromatography.

Selection of detection wavelength

The UV spectra of various diluted solutions of Itopride HCl in mobile phase were recorded using UV spectrophotometer. The peak of maximum absorbance was observed at 235 nm. This wavelength was used for detection of Itopride HCl.

Calibration curve for Itopride Hydrochloride:

Replicates of each calibration standard solutions (2, 4, 6, 8, 10 µg.mL⁻¹) were injected using a 20µL fixed loop system and the chromatograms were recorded. Calibration curves were constructed by plotting concentration of Itopride HCl on X-axis and peak areas of standard Itopride HCl on Y-axis and regression equations were computed for Itopride HCl. The calibration data is presented in Table 3.

Validation of the Proposed Method

The developed method of analysis was validated as per the ICH for the parameters like system suitability, specificity, linearity, precision, accuracy, robustness and system

suitability, limit of detection (LOD) and limit of quantitation (LOQ).

System suitability

System suitability tests are an integral part of chromatographic method which was used to verify reproducibility of the chromatographic system. To ascertain its effectiveness, certain system suitability test parameters were checked by repetitively injecting the drug solution at the concentration level 10µg.mL⁻¹ for Itopride HCl to check the reproducibility of the system.

At first the HPLC system was stabilized for 40 min. One blank followed by six replicates of a single calibration standard solution of Itopride HCl was injected to check the system suitability. To ascertain the systems suitability for the proposed method, the parameters such as theoretical plates, peak asymmetry, retention time and parameters were taken and results were presented in Table 1.

Specificity

The effect of wide range of excipients and other additives usually present in the formulations of Itopride HCl in the determinations under optimum conditions was investigated. The specificity of the RP-HPLC method was established by injecting the mobile phase and placebo solution in triplicate and recording the chromatograms. The common excipients such as lactose anhydrous, microcrystalline cellulose and magnesium stearate have been added to the placebo solution and injected and tested. The representative chromatogram of placebo was shown in Figure 2. The specificity results were presented in Table 5.

Linearity

The linearity graphs for the proposed assay methods were obtained over the concentration range of 2-10 µg.mL⁻¹ of Itopride HCl. Method of least square analysis was carried out for getting the slope, intercept and correlation coefficient, regression data values and the results were presented in Table 2 and Table 3. The representative chromatograms indicating the Itopride HCl were shown in Figure 5 to 9. A calibration curve was plotted between concentration and area response and statistical analysis of the calibration curve is shown in Figure 10.

Precision

Intraday and interday precision study of Itopride HCl was carried out by estimating corresponding responses 3 times on the same day and on 3 different days for the concentration of 10µg. The percent relative standard deviation (% RSD) was calculated which is within the acceptable criteria of not more than 2.0. The results for intraday and interday precision were presented in Table 6 and Table 7 respectively.

Accuracy (Recovery studies)

The accuracy of the method was determined by calculating recovery of Itopride HCl by the method of addition. Known amount of Itopride HCl at 50%, 100% and 150% was added to a pre quantified sample solution. The recovery studies were carried out in the tablet in triplicate each in the presence of placebo. The mean percentage recovery of Itopride HCl at each level was not less than 99% and not more than 101%. The results were presented in Table 8.

Robustness

The Robustness was evaluated by the analysis of Itopride HCl under different experimental conditions such as making small changes in flow rate (± 0.2 ml/min), detection wavelength (± 5 nm) and Mobile phase composition ($\pm 5\%$). The results were presented in Table 9.

LOD and LOQ

Limit of Detection is the lowest concentration in a sample that can be detected, but not necessarily quantified under

the stated experimental conditions. The limit of quantitation is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy. Limit of Detection and Limit of Quantitation were calculated using following formula $LOD = 3.3(SD)/S$ and $LOQ = 10 (SD)/S$, where SD = standard deviation of response (peak area) and S = slope of the calibration curve. The LOD and LOQ values are presented in Table 10.

Table 1: Optimized chromatographic conditions and system suitability parameters for proposed HPLC method for Itopride HCl

Parameter	Chromatographic conditions
Instrument	SHIMADZU LC-20AT prominence liquid chromatograph
Column	WELCHROM C ₁₈ Column (4.6 X 250mm, 5 μ m)
Detector	SHIMADZU SPD-20A prominence UV-Vis detector
Diluents	10mM Phosphate Buffer(pH-3): Acetonitrile (50:50 v/v)
Mobile phase	10mM Phosphate Buffer(pH-3): Acetonitrile (50 : 50 v/v)
Flow rate	1mL.min ⁻¹
Detection wave length	By UV at 235nm.
Run time	6 minutes
Column back pressure	128-130(kgf)
Temperature	Ambient temperature(25°C)
Volume of injection loop	20 μ L
Retention time (R _t)	2.650 min
Theoretical plates[th.pl] (Efficiency)	9,529
Theoretical plates per meter[t.p/m]	190583
Tailing factor (asymmetry factor)	1.154

Table 2: Linear regression data of the proposed HPLC method of Itopride HCl

Parameter	Method
Detection wavelength(λ max)	By UV at 235nm
Linearity range (μ g/ml)	2-10 μ g.mL ⁻¹
Regression equation (Y=a+bx)	Y=1.294+49.93X
Slope(b)	49.93
Intercept(a)	1.294
Standard deviation of slope (S _b)	0.177297583
Standard deviation of intercept (S _a)	1.073590179
Standard error of estimation (Se)	0.26045584
Correlation coefficient (r ²)	0.999
% Relative standard deviation* i.e., Coefficient of variation(CV)	0.13050
Percentage range of errors* (Confidence limits)	
0.005significance level	0.5466
0.001 significance level	0.8574

*Average of six determinations

Table 3: Calibration data of the proposed HPLC method of Itopride HCl

Concentration, μ g.mL ⁻¹	Retention time, (R _t) min.	Peak area, mV.s.
0	-	0
2	2.620	101.156
4	2.623	201.946
6	2.650	302.439
8	2.633	401.498
10	2.650	498.796

Table 4: Assay results of Itopride HCl formulation

Formulations	Labeled amount	Amount found	% Assay $\pm$ RSD*
GEPRIDE-50 (Intralabs Pvt. Ltd.)	50 mg	49.025 mg	98.05 $\pm$ 0.131

* Average of 6 determinations.

Table 5: Specificity study

Name of the solution	Retention time (R _t) min.
Mobile phase	No peaks
Placebo	No peaks
Itopride HCl 10 μ g.mL ⁻¹	2.650 min.

Table 6: Results of Precision study (Intraday)

Sample	Concentration ($\mu\text{g.mL}^{-1}$)	Injection no.	Peak area	% RSD (acceptance criteria < 2.0)
Itopride HCl	10	1	498.796	0.13050
		2	499.648	
		3	497.884	
		4	499.462	
		5	498.724	
		6	498.582	

Table 7: Results of Precision study (Interday)

Sample	Concentration ($\mu\text{g.mL}^{-1}$)	Injection no.	Peak area	% RSD (acceptance criteria < 2.0)
Itopride HCl	10	1	499.568	0.14877
		2	498.964	
		3	498.642	
		4	499.504	
		5	498.102	
		6	497.786	

Table 8: Recovery data of the proposed Itopride HCl by RP-HPLC method

Concentration level	Amount added ($\mu\text{g.mL}^{-1}$)	Amount found ($\mu\text{g.mL}^{-1}$)	Mean % Recovery $\pm$ SD*	% RSD [#]
50%	5	4.93	99.46 $\pm$ 0.0404	0.8126
	5	4.98		
	5	5.01		
100%	10	10.06	99.83 $\pm$ 0.0709	0.7106
	10	9.92		
	10	9.97		
150%	15	14.96	100.73 $\pm$ 0.1873	1.2399
	15	15.32		
	15	15.05		

*SD is standard deviation, [#] % RSD is percentage of relative standard deviation.

Table 9: Robustness results of Itopride HCl

Parameter	Optimized	Used	Peak area (mV.s)	Retention time (R_t), min	Plate count	Peak asymmetry
Flow rate ($\pm 0.2 \text{ mL.min}^{-1}$)	1.0 mL.min^{-1}	0.8 mL.min^{-1}	510.634	2.960	9680	1.220
		1.0 mL.min^{-1}	498.796	2.650	9529	1.154
		1.2 mL.min^{-1}	492.754	2.424	9348	1.074
Detection wavelength ($\pm 5 \text{ nm}$)	235 nm	230nm	482.584	2.652	9529	1.162
		235nm	498.796	2.650	9529	1.154
		240nm	486.540	2.651	9529	1.164
Mobile phase composition ($\pm 5\%$)	50:50v/v	55:45v/v	482.250	2.740	9678	1.182
		50:50v/v	498.796	2.650	9529	1.154
		45:55v/v	486.786	2.490	9472	1.167

Table 10: Limit of Detection (LOD) and Limit of Quantitation (LOQ)

Limit of Detection(LOD)	0.098028425 $\mu\text{g.mL}^{-1}$
Limit of Quantitation(LOQ)	0.297055832 $\mu\text{g.mL}^{-1}$

Figure 1: Structure of Itopride HCl

Figure 2: Chromatogram of placebo

Figure 3: A typical chromatogram of Itopride HCl standard

Figure 4: Chromatogram of market formulation (GEPRIDE-50 Tablets) of Itopride HCl

Figure 5: Standard chromatogram of Itopride HCl (2 µg.mL⁻¹)

Figure 6: Standard chromatogram of Itopride HCl (4 µg.mL⁻¹)

Figure 7: Standard chromatogram of Itopride HCl (6 µg.mL⁻¹)

Figure 8: Standard chromatogram of Itopride HCl (8 µg.mL⁻¹)

Figure 9: Standard chromatogram of Itopride HCl (10 µg.mL⁻¹)

Figure 10: Calibration plot of Itopride HCl

RESULTS AND DISCUSSION

The mobile phase consisting of 10mM phosphate buffer (pH-3.0): acetonitrile (50:50 % v/v at 1mL.min⁻¹ flow rate was optimized which gave sharp peak, minimum tailing factor with short run time for Itopride HCl. The retention time for Itopride HCl was 2.650 min. UV spectra of Itopride HCl showed that the drug absorbed maximum at 235 nm, so this wavelength was selected as the detection wavelength. System suitability parameters & optimized chromatographic conditions are shown in Table 1. The calibration curve for Itopride HCl was found to be linear over the range of 2-10 µg.mL⁻¹. The data of regression analysis of the calibration curve is shown in Table 2 and Table 3.

The developed method was applied to the assay of Itopride HCl tablets. The experimental results are given in Table 4. The results were very close to labeled value of commercial tablets. The representative standard and sample chromatograms of Itopride HCl are shown in Figure 3 and 4 respectively. The regression equation was found to be $Y=49.93X + 1.294$ with correlation coefficient is $r^2=0.999$ which indicates this method has good linearity. The representative chromatograms indicating the Itopride HCl are shown in Figure 5 to 9. The linearity of the graph is shown in Figure 10. The specificity was studied for the examination of the presence of interfering components, while the comparison of chromatograms there was no interference from placebo (Fig 2) with sample peak. They do not disturb the elution or quantification of Itopride HCl, furthermore the well-shaped peaks also indicate the specificity of the method. Therefore, it was concluded that the method is specific. The specificity results are summarized in Table 5. Precision was studied to find out intra and inter day variations in the test methods of Itopride HCl for the three times on the same day and different day. The %RSD for intra-day and inter-day precision obtained was 0.13050 and 0.14877 respectively. The % RSD (< 2.0) indicates that the proposed method is quite precise and reproducible and results are shown in Tables 6 and 7. Recovery studies of the drug were carried out for the accuracy parameter at three different concentrations levels i.e., multiple level recovery studies. A known amount of Itopride HCl standard was added into pre-analyzed sample and subjected them to the proposed HPLC method. The % recovery was found to be within the limits as listed in Table 8. Generally the mean percentage recovery of Itopride HCl at each level was not less than 99% and not more than 101%. In this case percentage recovery of Itopride HCl was found to be in the range of 99.46 % to 100.73%. The method precision was done and the low %RSD (0.130) values indicates that the proposed method which was in good agreement with precision. Robustness was done by small changes in the chromatographic conditions like mobile phase flow rate, temperature, mobile phase composition etc.,. It was observed that there were no marked changes in the chromatograms. Infact the parameters are within the limit which indicates that the method has robustness and suitable for routine use. The Robustness results are presented in Table 9. The limit of detection (LOD) and limit of quantitation (LOQ) was calculated based on the standard deviation (SD) of the response and the slope (S) of the calibration curve at levels approximating the LOD and LOQ. The limit of detection (LOD) was 0.09802 µg.mL⁻¹ and the limit of quantitation

(LOQ) was 0.297µg.mL⁻¹ which shows that this method is very sensitive. The results are presented in Table 10.

CONCLUSION

A New validated RP-HPLC method has been developed for the quantitative determination of Itopride HCl in bulk and pharmaceutical tablet dosage forms. Statistical analysis of the results shows that the proposed procedure has good precision and accuracy. The method was completely validated shows satisfactory results for all the method validation parameters tested and method was free from interference of the other active ingredients and additives used in the formulation. Infact results of the study indicate that the developed method was found to be simple, reliable, accurate, linear, sensitive, economical, and reproducible and have short run time which makes the method rapid. Hence it can be concluded that this method may be employed for the routine quality control analysis of Itopride HCl in active pharmaceutical ingredient (API) and pharmaceutical preparations.

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