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[1]Spectrophotometric determination of Cisapride Based on ion-pair complex formation with Bromophenol blue

التقدير الطيفي للسيزابرايد بالاعتماد على تكوين معقد مزدوج أيوني مع كاشف بروموفينول الازرق

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Abstract:

A new simple, sensitive and inexpensive method has been developed for the spectrophotometric determination of cisapride in pharmaceutical formulation. The turbidimetric method is based on the formation of the ion-pair complex between the drug and bromophenol blue (BPB) in presence of potassium chloride at pH= 2.6, with a maximum absorbance at 520 nm. The calibration graph is linear in the concentration range 5-50µg.ml^{-1}, with good correlation coefficient (r = 0.9989).The limit of detection was found to be 1.14 µg.ml^{-1} and no interference was observed from common excipients in the pharmaceutical preparation that contain cisapride with good accuracy and precision.

الخلاصة :

تم تطوير طريقة بسيطة وحساسة للتقدير الطيفي لعقار السيزابرايد في المستحضرات الصيدلانية. أعتمدت الطريقة التعكيرية المتبعة في تكوين مزدوج أيوني بين العقار مع كاشف بروموفينول الازرق بوجود كلوريد البوتاسيوم وعند دالة حامضية مقدارها (2.6) حيث أظهر المعقد المتكون اعظم امتصاصية عند الطول الموجي (520 nm) . وعند تطبيق الطريقة تحت الظروف المثلى كانت امتصاصيات تراكيز العقار التي تتراوح بين (5-50)µg.ml^{-1} مطاوعة لقانون بير حيث كان معامل الارتباط (r=0.9989) .
وكان حد الكشف مساو الى 1.14 µg.ml^{-1} . لم تظهر المضافات التي تستخدم عادة لتحضير جرع العقار التي تمت دراستها اي تداخلات طيفية في تقدير العقار وكانت جميع النتائج المستحصلة في تطبيق الطريقة دقيقة ومتوافقة .

Introduction:

Cisapride is, chemically, 4-amino-5-chloro-N-[1[3-(4-fluoro-phenoxypropyl]-3-methoxy-4-piperidinyl]-2-methoxy benzene amide, a gastrointestinal (GI) prokinetic agent that has been widely used in adults and children for the treatment of upper GI motility disorders such as gastrointestinal reflex disease nonulcer dyspepsia and gastroparesis[1,2]. Cisapride has gained popularity as a prokinetic agent primarily because it is devoid of antidopaminergic effects and, therefore, has less psychomotor adverse effects when compared with older prokinetic drugs such as metoclopramide.[2] In order to assure the quantity of cisapride in dosage forms, several methods were described for determination of drugs in pharmaceutical formulations. Chromatographic methods have been reported for quantitative determination of cisapride in dosage forms, bulk drugs and process monitoring of cisapride by RP- HPLC.[3-5] Cisapride was also determined in pharmaceutical formulations by electrochemical techniques such as square wave voltammetry[6]. Cisapride has also been determined spectrophotometrically based on the coupling of the diazotised drug with acetylacetone in alkaline medium [7] and with chromotropic acid, phloroglucinol and N(1-naphthyl) ethylene-diamine dihydrochloride[8] to give coloured products having maximum

absorbances of 530 and 540 nm respectively. On the other hand, cisapride was also determined upon using derivative spectrophotometry by measuring the 10-values at 264, 300 nm and 20-values at 276, 290 nm and 276-290 nm respectively [9]. In the present work the same idea present by kanakapura et.al[10] for the spectrophotometric determination of cyproheptadine which based on the formation of ion pair so attempts to determine cisapride with bromophenol blue (BPB) under slightly altered condition of pH, ionic strength and reagent concentration to form an insoluble ion-pair complex. The resulting suspension is measured at 520 nm, also, the proposed method provide economic procedure and most simple and reliable spectrophotometric method for their determination either pure form or in formulation.

Experimental:

Instrumentation:

Absorbance measurements were carried out using a single beam UV-Vis spectrophotometer from Beckman Scientific equipment model DU-65 and 10mm glass cells were employed for all spectral measurements. The pH values of all measured solutions were measured using pH-meter DW-9421 from Philips instrument.

Materials and reagents:

All chemicals used were of analytical grade. The standard powder cisapride purity (99.9%) was kindly supplied by the State Company for Drug Industries and Medical Appliances Samara-Iraq (SDI). Bromophenol blue (BPB) 7.45×10^{-4}M solution was prepared by dissolving 50mg of the reagent in 25ml of ethanol and completed to 100ml by distilled water. Potassium chloride 0.5M solution, prepared by dissolving 3.73gm in water and diluting to 100ml in a volumetric flask. Hydrochloric acid 0.1M solution prepared by diluting 4.25 ml of concentration acid to 500 ml.

Standard drug solution:

An accurately weighed amount of drug cisapride equivalent to 100 mg of the base was dissolved in a bout 75 ml absolute ethanol and made up to volume into 200 ml volumetric flask with 0.1M HCl to provide 500 $\mu g.ml^{-1}$ stock standard solution of the base. This was diluted to obtain suitable concentrations that lie in the linear range of proposed assay method.

Procedure Assay:

Aliquot portions of the standard cisapride solution in the concentration range of 5.0-50 $\mu g.ml^{-1}$ were transferred to a series of 10 ml volumetric flasks then 0.25 ml of 0.1 M HCl and 0.8 ml of KCl were added and the total volumes were adjusted to about 8ml by adding water and mixed well, 0.20 ml of BPB reagent was then added to each solution, and the volumes were made up to 10 ml. The flasks were then shaked for 1 min. and allowed to stand for 10 min. at room temprture. The absorbances were measured at 520 nm against the corresponding reagent blank.

Procedure for dosage forms:

Twenty cisapride tablets were chosen randomly from a total number of 50. An accurately weighed quantity of drug are ground into a fine powder and an amount of powder equivalent of approximately 100 mg of the cisapride was accurately weighed and dissolved in about 75 ml of absolute ethanol and made up to volume into 200 ml volumetric flask with 0.1 M HCl to provide 500 $\mu g.ml^{-1}$. The solution was filtered using a Whatman No.42 filter paper. The first 10ml portion of the filtrate was rejected and the filtrate was used in the spectrophotometic determination after appropriate dilution.

Results and discussion:

The cisapride solution reacted with BPB solution in acidic medium solution to form a suspension which can be used for determination of the citied drug in dosage form. The drug-dye ion-pair formation exhibits an absorption maximum at 520 nm against reagent blank (Fig.1).

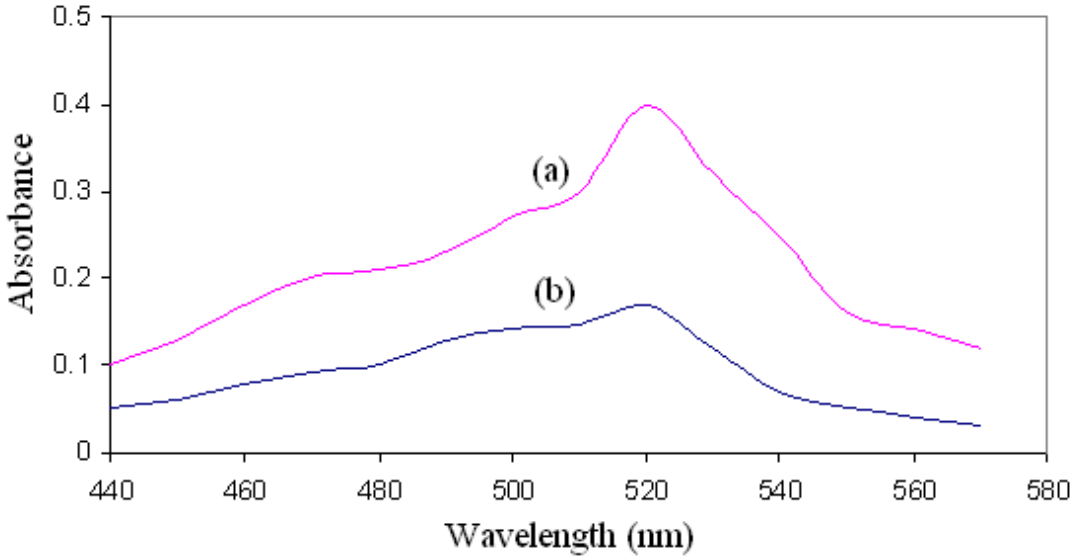


Fig.(1): Absorption spectra of :-
(a)suspension 40 µg.ml^{-1} cisapride, BPB = 2.23 × 10^{-5} M, KCl = 0.04 M at pH=2.6
(b) Reagent blank 2.23 × 10^{-5}M BPB , KCl=0.04M at pH = 2.6
against distilled water.

Optimization of experimental variables:

The influence of various factors on the development and stability of the formation of turbid suspension was studied to determine the optimal conditions, viz, pH, reagent concentration ionic strength and time of reaction.

Effect of pH:

While studying the effect of pH, the drug-dye ion pair formation was found to be critically dependent on the pH of the solution. The influence of pH on the development of the ion pair was systematically investigated from pH 2.0-4.0. The pH of solution was adjusted with a few drops of 0.1 M HCl and 0.1 M NaOH. Lower pH values 2.0-2.4 resulted in the coprecipitation of the dye. The addition of NaOH to an acidic suspension resulted in a complete dissolution of the solid at pH above 4.0. Hence a pH of 2.6 was selected in all the subsequent experimental work (Fig.2).

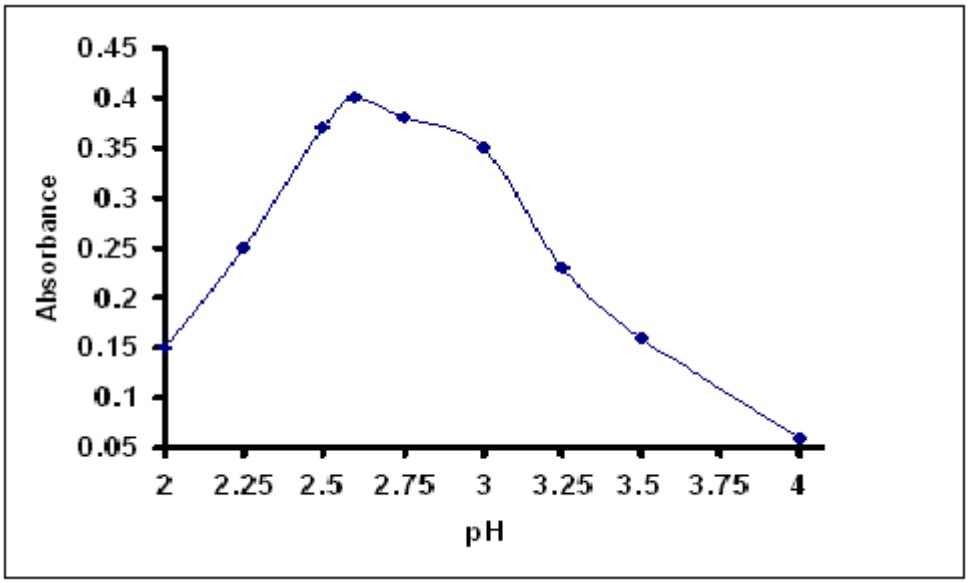


Fig. (2): Effect of pH on the absorbance of 40 µg/ml cisapride, 2.23×10^{-5} BPB at 520 nm.

Effect of ionic strength:

In order to verify the contribution of the ionic strength on the formation of the ion-pair, the influence of ionic strength was studied by adjusting the concentration of KCl in the solution to values ranged from 0.01-0.07 M by adding different volumes of 0.5 M of the salt.

It was observed that ionic strength values at 0.04 M resulted in a maximum coprecipitation of the reagent. 0.04 M of the salt solution was used in the reaction mixture (Fig.3).

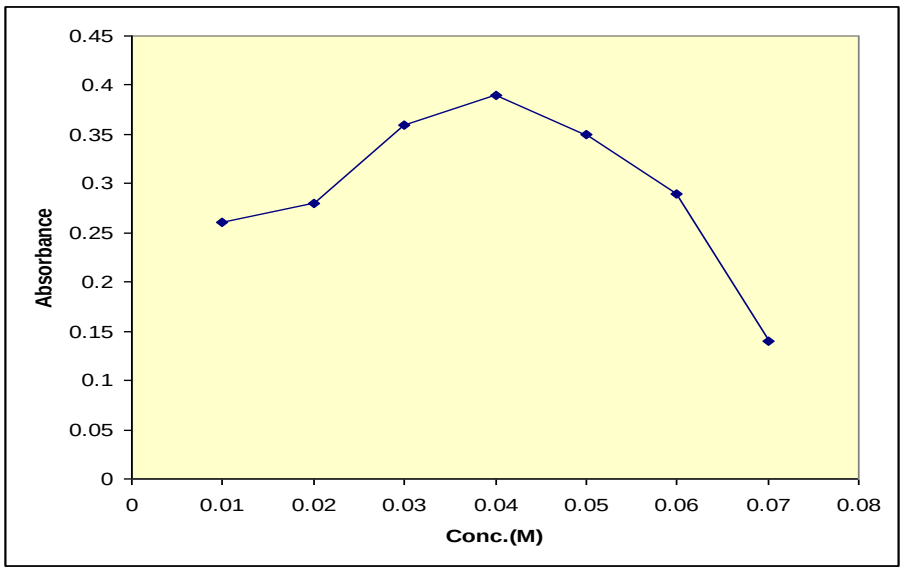


Fig.(3): Effect of ionic strength 40 µg/ml cisapride, 2.23×10^{-5} BPB,pH =2.6

Effect of reagent concentration:

Various volumes of BPB solution were added to 40 µg.ml^{-1} of cisapride solution, 0.20 ml of 2.23×10^{-5} M of BPB was found to be a final assay solution selected for the net absorbance. An increase in reagent concentration causes a decrease in absorbance which may be due to the formation of new species (Fig.4).

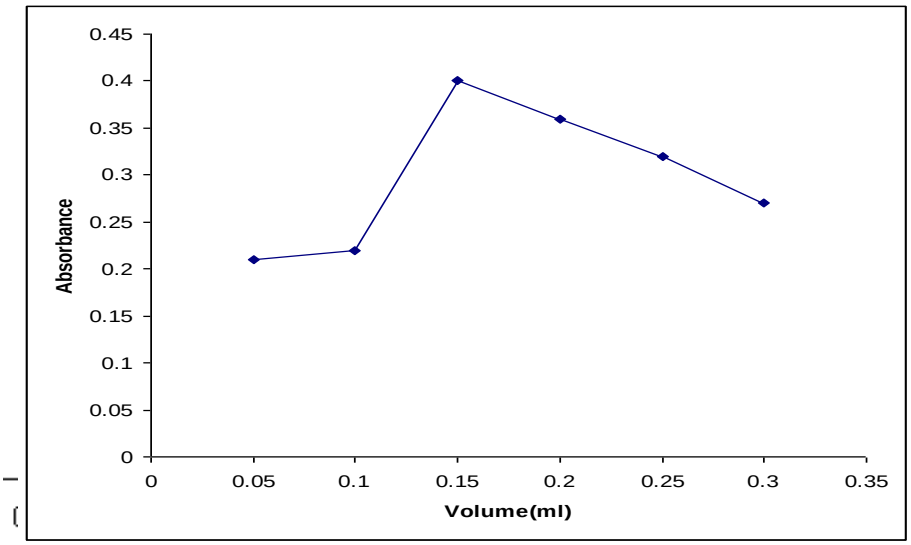


Fig.(4): Effect of reagent volume on the absorbance of 40 µg/ml^{-1} cisapride, solution.

Stability of suspension:

The optimum reaction time for stability of suspension was determined after shaking for 1 min by keeping the solutions at room temperature , and then recording their absorbance values. A continuous increase in the absorbance occurred in the first 10 min, after that the absorbance started to decrease. However, it is advisable to measure absorbance readings 10 min after the addition of the dye.

Stoichiometry of the complex:

Job's method of continuous variation was used to determine the molar ratio of cisapride - bromophenol blue ion pair (Fig5). The results obtained show that 1:1 cisapride to bromophenol blue complex was formed at 520 nm, therefore the formation of the complex can be represented as in following scheme. [11, 12]

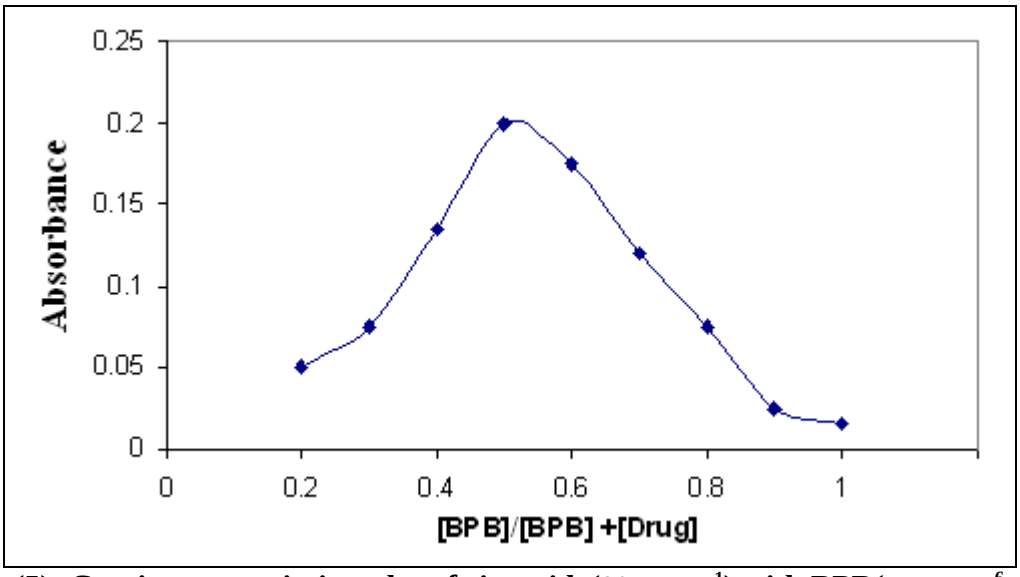
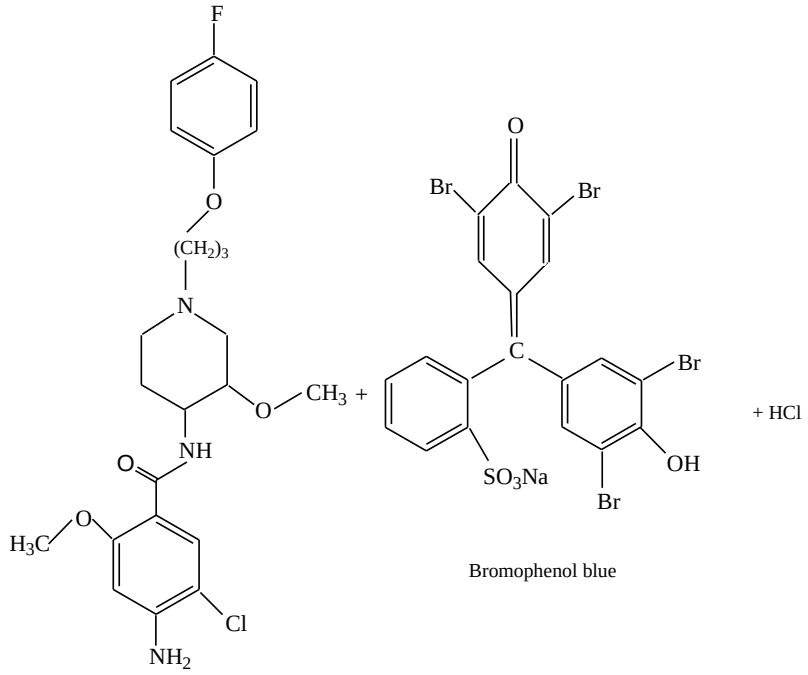


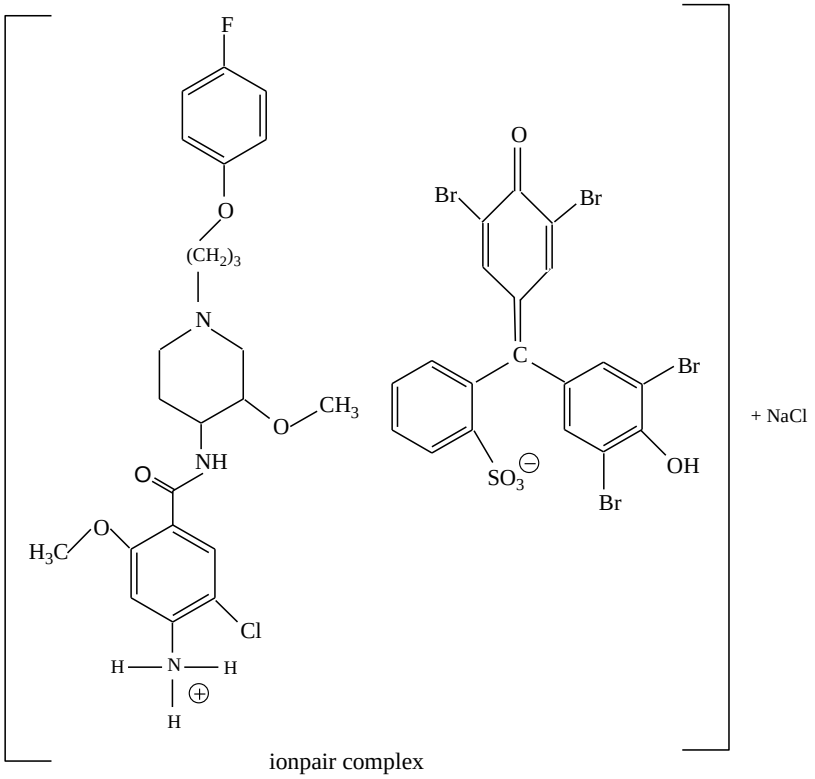
Fig.(5): Continuous variation plot of cisapride(30 µg.ml^{-1}) with BPB(1.48 ×10^{-6}M).



Cisapride

Bromophenol blue

+ HCl



ionpair complex

+ NaCl

Analytical data for the suggested method:

A linear relation was found between absorbance at λ_{max} and concentration of cisapride in the range shown in (Fig.6).
The calibration graph could be described by the equation
Abs. = 0.0076 + 0.0096 [Conc. Of Cisapride ($\mu g.ml^{-1)}$]
The limit of detection (LOD) and lower limit of quantitation (LOQ) were also given in (Table1), respectively.

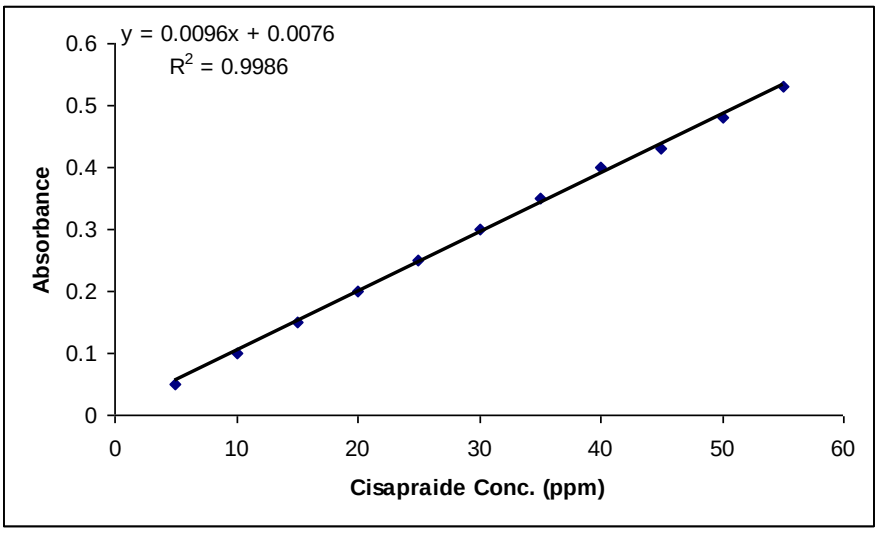


Fig. (6): Calibration Curve.

Table (1): Analytical data for turbidimetry method.

Parameter	**Proposed method**
λ_{max} , nm linear dynamic range ($\mu g.ml^{-1}$) Limit of detection (LOD) $\mu g.ml^{-1}$ Limit of quantitation (LOQ) $\mu g.ml^{-1}$	520 5-50 1.147 3.478
Regression equation, y intercept (a) = 0.0076 slope (b) = 0.0096 correlation coefficient (r) = 0.9986	

Accuracy and precision:

The accuracy of the method was established by performing five replicate analyses on pure drug solutions at three different concentration levels within the Beer's law limits of the drug and calculating the percentage error. The precision was ascertained by calculating the relative standard deviation percent (%RSD) for five determinations at each level. Both results are given in (Table 2), which reveal that the method is reasonably accurate and precise.

Table (2) : Evaluation of the accuracy precision of the proposed method.

	Amount taken µg.ml^{-1}	Amount found µg.ml^{-1}	Error%	%RSD
Cisapride studied	20	20.01	0.05	2.53
	30	29.01	3.30	1.41
	45	46.51	3.30	4.20

Interference studies:

The effect of common excipients that often accompany the studied drug in various pharmaceutical tablets were tested for possible interference in the assay. Samples were prepared by mixing known amount 25 µg.ml^{-1} of cisapride with various amounts of the common excipients such as talc (5 mg), starch (7 mg), lactose (10 mg), gelatine (40 mg), magnesium stearate (20 mg) and sodium alginate (25 mg). The results are presented in (Table 3). The percentage recovery was found to be in the range 98.2-101.1 with RSD values ≥ 1.81 for three replicate.

Table (3): Determination of Cisapride (*) in the presence of excipients.

Material	Tolerance limit µg.ml^{-1}	% Recovery of cisapride ± R.SD(**)
Talc	500	99.92 ± 0.27
Starch	750	99.91 ± 0.64
Lactose	1000	100.1 ± 1.11
Eglantine	4000	99.82 ± 0.32
Magnesium stearate	2000	98.82 ± 1.80
Sodium alginate	2500	101.1 ± 0.91

***** 25 µg.ml^{-1} of cisapride taken

****** Average of three replicate

Application of the method to the analysis of tablets:

The obtained satisfactory validation results made the proposed procedures suitable for the routine quality control analysis of cisapride. The results, presented in (Table 4), reveal that the recoveries were in the range of 94.66 to 100.20%, reflecting high accuracy and precision of the proposed method as indicated by low RSD values.

Table (4): Results of assay of formulation by the proposed method.

Formulation Brand Name	labeled amount mg/ tablet	Amount found mg/table	% Recovery ± R.S.D *
Cisapride•	10	9.61	94.66 ± 0.91
Propulsid••	10	10.11	100.20 ± 0.61
Propulsin•••	10	9.91	99.68 ± 0.97

***** Average of four determination

• Marked by S.D.I, Iraq.

•• Marked by Cipla and Merind, India.

••• Marked by HM-Holden BV-Holland.

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