

## Spectrophotometric Determination of Ranitidine-HCl in Pure Form and Pharmaceutical Formulations with Metol and potassium hexacyanoferrate (III)

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### الخلاصة

طريقة بسيطة عالية الحساسية وذات دقة عالية لتقدير الرانيتدين بشكل نقي او في المستحضرات الصيدلانية من خلال تكوين معقد تضمنت الطريقة تفاعل الرانيتدين مع مزيج الميتول وبوتاسيوم سداسي سيانيد الحديد و تكوين معقد ملون لتقدير الرانيتدين طيفيا عند اقصى طول موجي ٥٤٠ نانوميتر تم تحديد الظروف الفضلى للتفاعل للحصول على اعلى حساسية و اطول استقرارية عند الظروف الفضلى للامتصاصية للمعقد الملون وجد زيادة بالخطية مع ازدياد تركيز الرانيتدين والموثق من خلال قيمة معامل الارتباط ٠.٩٩٩٥ ذي التركيز المستخدم من (٢-٩٠) مايكرو غرام/مل وبحدود كشف (٠.٠٩٨٨) مايكرو غرام/مل وبانحراف نسبي (٠.٧١) . طبقت الطريقة المقترحة بدقة وضبط عالي وب نجاح لتقدير نسبة الرانيتدين بشكل نقي اوفي المستحضرات الصيدلانية وتم مقارنة النتائج الاحصائية باستخدام اختباري  $F+t$  وقد وجد ان قيمهما اقل من قيمهما الواردة بالطريقة المستخدمة بالدستور البريطاني .

### Abstract

A simple, sensitive and accurate spectrophotometric method of determination of Ranitidine-HCl (RNH) in pure form and its pharmaceutical formulation. Was used in this study The method is based on the formation of (RNH) complex. The reaction between the Ranitidine-HCl with the mixture of metol and potassium hexacyanoferrate (III) was evaluate metol ( N-methyl - p - aminophenosulphate ) for the spectrophotometric determination of the Ranitidine - HCl . The maximum absorbance of the colored complex occurred at  $\lambda = 540\text{nm}$ . Reaction conditions have been optimized to obtain (RNH) complex of high sensitivity and longer stability. Under optimum conditions the absorbance of the (RNH) complex where found to increase linearly with the increase in concentration of the Ranitidine-HCl which corroborated with correlation coefficient value. Of 0.09995 with concentration ranges of (2-90)  $\mu\text{g/ml}$  relative standard deviation and relative error of prediction for drug were lower . The proposed method was successfully applied to determine of the selected Ranitidine-HCl in pure form and pharmaceutical formulations with good precision and accuracy compared to standard method as revealed by t- and F- values , the results obtained agree well with the labeled contents.

### Introduction

Ranitidine hydrochloride (RNH), chemically N, N dimethyl-5-(2-(1-methylamine-2-nitrovinyl)-ethylthiomethyl) furfurylamine hydrochloride. It is a H<sub>2</sub>-receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hypersecretory conditions . It acts by blocking histamine receptors which are present on the cells in the stomach lining. Ranitidine binds to H<sub>2</sub> receptors, replacing some of the histamine. As a result, the amount

of stomach acid produced by these cells is decreased. Ranitidine decreases the amount of acid in the stomach and duodenum. Ranitidine helps relieve the symptoms of indigestion and aids the healing of ulcers. It is also used to depress acid production in various other conditions [1]. The molecular formula is C<sub>13</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S·HCl, representing a molecular weight of 350.87 g mol. It is a white to pale yellow, crystalline substance that is soluble in water.

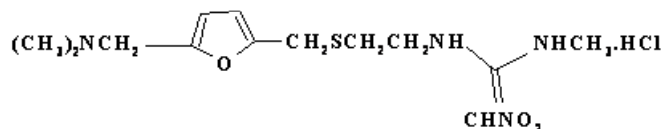


Fig. 1: Structural formula of RNH drug

Several methods have been reported for the determination of Ranitidine-HCl in bulk, pharmaceutical dosage forms, and biological fluids[2].

These methods include kinetic spectrophotometry [3,4], HPLC[5,6], HPTLC[7], Micellar liquid chromatography[8], liquid chromatography mass spectrometry[9,10], liquid chromatography[11], capillary electrophoresis [12], fluorimetry[13], flow injection analysis[14,15], voltammeter[16], potentiometer[17,18], polarography[19], hanging mercury drop electrode[20], FT-IR[21], AAS[22], argentimetric[23], titrimetry[24] and UV-spectrophotometry[25]. But such techniques are time consuming because extensive sample pretreatment, required expensive instrumentation and beyond the reach of small laboratories, particularly in under developed and developing countries. The aim of the present work is to study the charge – transfer complex reaction in developing simple, accurate, sensitive and reproducible assays to determination Ranitidine-HCl in pure form and pharmaceutical formulation [26].

## 2. Experimental

### Apparatus

UV-1600 PC (Shimadzu, Japan) UV Spectrophotometer with matched 1cm quartz cells were used for all measurements.

### Materials and Reagents

All reagents used were analytical grade and water was always double distilled. Pure samples Ranitidine-HCl pure grade was provided by SID- Samara factory. Standard stock solutions Stock solutions of Ranitidine-HCl were prepared by dissolved (0.01g) of Ranitidine-HCl in 50 ml volumetric flasks and diluted to the mark with distilled water.

### Market samples

Ranitidine-HCl tablets, labeled to contain (20%) were obtained from commercial sources in the local market.

### Reagents

Metol solutions (13 and 20mM) were freshly prepared by dissolved (0.225g) and (0.68889g) of metol respectively, and diluting to 50ml with distilled water in volumetric flasks. (20mM) potassium hexacyanoferrate (III) were prepared by dissolved (0.332 g)  $K_3[Fe(CN)_6]$  and diluting to 50 ml with distilled water in volumetric flask.

### Recommended analytical procedure Method

0.1-10  $\mu\text{g}$  /ml of different aliquots of Ranitidine-HCl standard stock (100  $\mu\text{g}$  /ml) were transferred into a series of 10 ml volumetric flasks, To each these were added 1ml of buffer solution (pH= 5.2) & metol 1ml and potassium hexacyanoferrate (III) (1ml) were diluted to the mark with distilled water. The absorbance was measured at  $\lambda=540\text{nm}$  against a reagent blank prepared

similarly. A calibration graphs were drawn by plotting the absorbance against the drug concentration.

### Analytical of pharmaceutical formulation

Ten tablets were accurately weighted and finally powdered. An amount of the powder equivalent (10mg) Ranitidine-HCl was dissolved in 100ml with distilled water of calibrated flask. The contents of the flask were shaken and then make up to the mark with distilled water to obtain (100  $\mu\text{g}/\text{ml}$ ) of RHN.

## Results and Discussion

Absorption spectra Throughout the preliminary investigation on the reaction[15], between drugs (RHN) with metol in the presence of potassium hexacyanoferrate (III), (violet colored) products obtained (Scheme-1) with a maximum absorption at  $\lambda=540\text{nm}$  (Fig. 2). The absorbance of the colored products measured against reagent blank which has minimum absorbance at the same wavelength from the results obtained, appeared that it is possible to determine no. of micrograms of this drug.

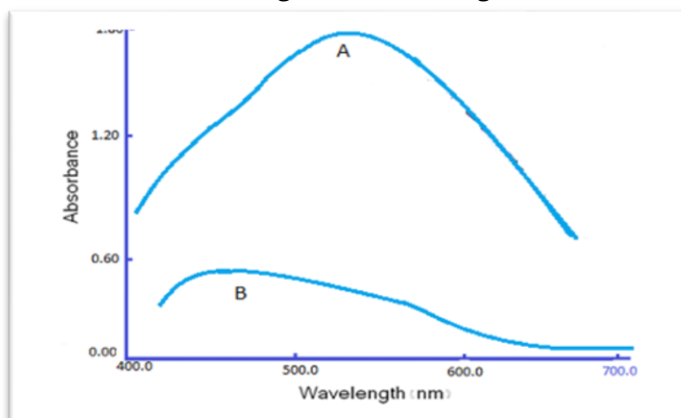
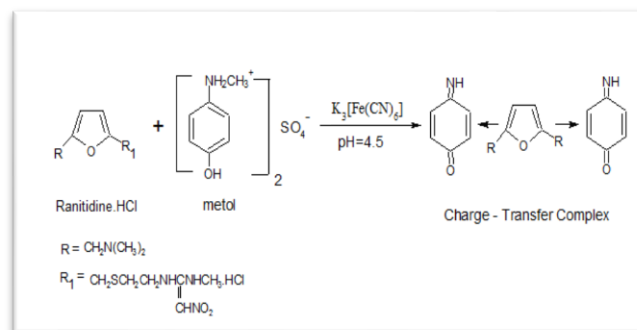


Fig. 2. Absorption spectra of A= drug Ranitidine-HCl complex, B= metol/ potassium hexacyanoferrate (III) reagent



Scheme – 1

### Optimization of Experimental Conditions

The effect of various variables on the color development was tested to establish the optimum conditions for the determination of Ranitidine-HCl by using metol and potassium hexacyanoferrate (III).

#### Effect of pH

The optimum pH for complete color development is (5.2)fig-3The buffer solution(0.1M KHphthalate+0.1M HCL) is added to give the required pH.

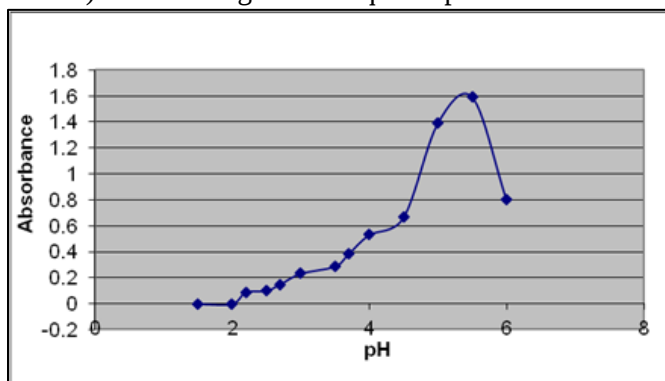


Fig. 3.Optimum pH for complete color development

#### Effect Concentration of potassium hexacyanoferrate (III)

The effect of the different volumes of (20mM) of  $K_3[Fe(CN)_6]$  solution was examined on the maximum absorbance of the color product in the presence of (1ml) metol (20mM). Fig. 5 shows that 1 ml of the solution of potassium hexacyanoferrate (III) was enough to obtain the maximum absorbance.

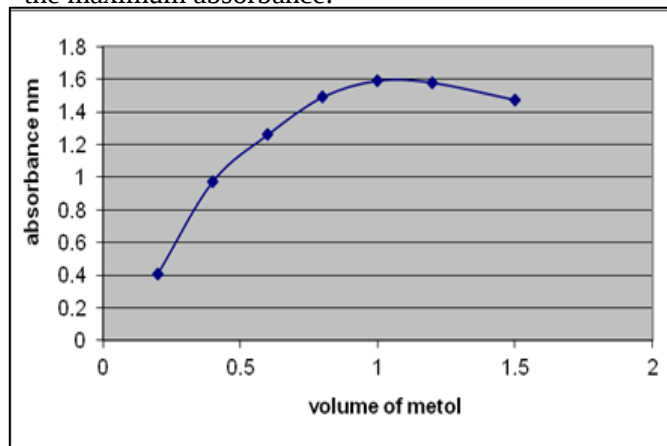


Fig. 4. Effect of volume of (20mM) potassium hexacyanoferrate (III) on the absorbance intensity of Ranitidine-HCl drug at 540nm

#### Effect volume of metol reagent

Metol was found to be a useful for charge transfers reaction, because it was produced a stable charge transfer complexes rapidly with drugs in prescence of potassium hexacyanoferrate (III). More over this reagent is easily obtainable and is soluble in water. The effects of the different volumes of (20mM) metol solutions were examined on the maximum formation of the color product. Fig.6 shows that ( 1ml) of the solution was enough to obtain the maximum absorbance, and it was used in the subsequent experiments.

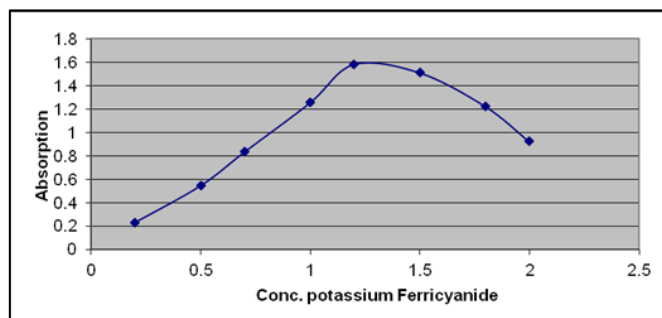


Fig- 5:Effect of volume of metol reagent (20 mM) on the absorbance intensity of Ranitidine-HCl drugusin (1ml) of potassium hexacyanoferrate at 540nm

#### Effect of addition Orders

Seven orders of addition were examined as shown below in table-1:

Table 1: effect of series addition

| NO. | Addition order | Absorbance(nm) |
|-----|----------------|----------------|
| 1   | F+M+D+B        | 0.320          |
| 2   | F+B+D+M        | 0.377          |
| 3   | F+M+B+D        | 0.410          |
| 4   | B+D+M+F        | 0.650          |
| 5   | M+F+B+D        | 0.520          |
| 6   | M+B+D+F        | 0.612          |
| 7   | D+B+M+F        | 0.773          |

D= Drug, R= Reagent (metol), O= Oxidant  $k_3[Fe(CN)_6]$ , B=buffer

#### Effect of temperature

The effect of temperature on the color intensity of the product was studied Fig. 7 in practice a maximum absorbance was obtained when the color was developed at room temperature (25°C), but when the color was developed in an ice bath (5°C) or in a water bath (45°C)

a loss in color and instability were observed. It is therefore recommended that the color reaction should be carried out at room temperature (25°C) after 20min.(Fig-8)

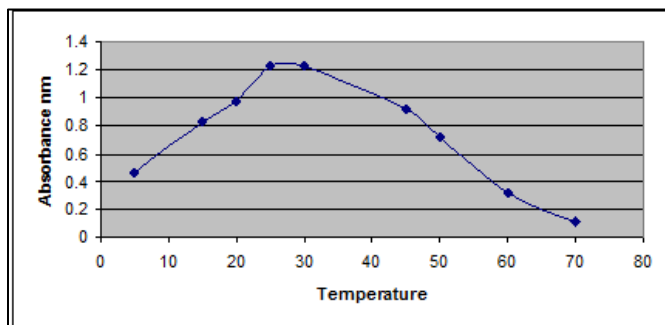


Fig.6 Effect of temperature of the valu absorbance at 540nm

### Effect of time stability

The color intensity reached a maximum after drug solution had been reacted immediately with metol and potassium hxacyanoferrate (III) in aqueous medium and became stable after (20min), remained stable for at least (Fig.8).

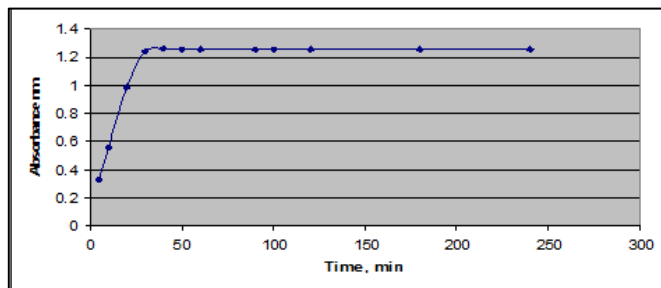


Fig.7 Effect of time (min) on the absorbance of the formed complexes of Ranitidine-HCl drug at 540nm

### Calibration Graph

After the optimizing reactions describe above, calibration curve (Fig.9) for Ranitidine-HCl was constructed by plotting absorbance of Ranitidine-HCl complex and the concentration of the Ranitidine-HCl drug. The calibration curve was linear. The analytical values of statistical treatments for the calibration curve are summarized in table-2.

Table-2: performance analytical data of the proposed method

| Parameter                                                             | Value               |
|-----------------------------------------------------------------------|---------------------|
| Correlation coefficient @                                             | 0.9995              |
| Linearity percentage ( $r^2$ %)                                       | 99.950              |
| Test for a significant correlation (t)                                | 154.906             |
| Regression equation                                                   | $Y=0.0710X+0.1174$  |
| Slope ( $\text{ml } \mu\text{g}^{-1}$ )                               | 0.010               |
| Intercept                                                             | 0.117               |
| Standard deviation of the residuals                                   | 0.001057166         |
| Standard deviation of the slope, $S_b$                                | 0.001               |
| Standard deviation of intercept $S_a$                                 | 0.003               |
| Linearity range ( $\mu\text{g ml}^{-1}$ )                             | 2-900               |
| Molar absorptivity, $\epsilon$ ( $\text{l mol}^{-1} \text{cm}^{-2}$ ) | $3.144 \times 10^5$ |
| Sandell's sensitivity, $S$ ( $\mu\text{g cm}^{-2}$ )                  | $1 \times 10^{-3}$  |
| Limit of detection LOD ( $\mu\text{g ml}^{-1}$ )                      | 0.098               |
| Limit of quantification LOQ ( $\mu\text{g ml}^{-1}$ )                 | 0.988               |

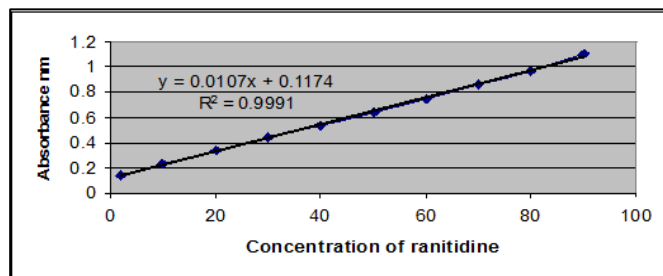


Fig.8. Calibration Curve of Ranitidine-HCl

### Accuracy and precision

The accuracy and precision of the determination of Ranitidine-HCl were studied depending upon the value percentage of the relative error (E%), recovery (REC%) and relative standard deviation (RSD%) . For five replicates of each concentration of Ranitidine-HCl (8, 16, 25)  $\mu\text{g.ml}^{-1}$ . The results in Table 3 show a good accuracy and precision.

Table-3: Accuracy and precision of the proposed method  
Average of five determinations

| NO. | Concentration $\mu\text{g/ml}$ |        | E%*     | REC%*   | RSD%* |
|-----|--------------------------------|--------|---------|---------|-------|
|     | present                        | Found  |         |         |       |
| 1   | 8.000                          | 8.028  | 0.350   | 100.350 | 0.143 |
| 2   | 16.000                         | 15.887 | - 0.711 | 99.289  | 0.266 |
| 3   | 25.000                         | 25.011 | 0.044   | 100.044 | 0.123 |

### Stoichiometry of the formed product

the stoichiometry of the formed product was investigated by mole ratio and continuous variation (Job's method), and slope ratio methods .In the mole

ration method increased volumes of (20 mM)metol were added to a (1 ml) of (20mM) Ranitidine-HCl in a series of (10ml) volume flasks, followed by 1ml of 20mM potassium hexacyanoferrate (III), the volumes were made up to the mark with distill water, allowed to stand to 15 min. and the absorbance were measured at 540 nm versus the reagent blanks. The results were plotted as shown in (Fig.10-11) which indicated the existence of 1:1 metol: Ranitidine-HCl.

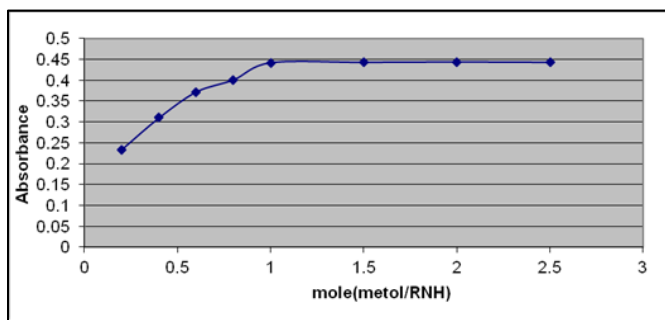


Fig. 9. Mole ratio plot

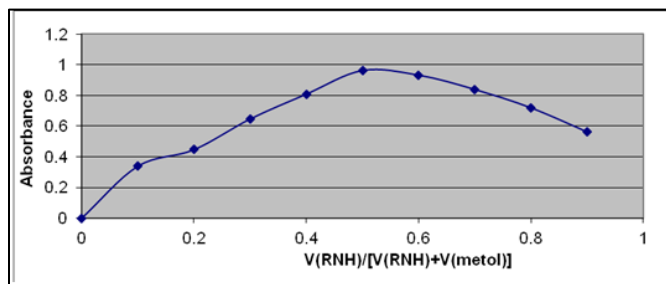


Fig. 10: Continuous variation plots

## Pharmaceutical application

### Evaluation of the proposed method

The proposed method was applied to the determination of Ranitidine-HCl (tablet) in proprietary drugs purchased from local stores. The results, shown in Table 4, suggest that the method is suitable for the determination of aspirin and that the excipient in the dosage forms do not interfere.

Table4. Application of the proposed to determination of Ranitidine-HCl in pharmaceutical tablet

| Pharmaceutical Tablet   | Conc. µg/ml |        | E%*    | Rec%*   | RSD%* |
|-------------------------|-------------|--------|--------|---------|-------|
|                         | Present     | Found  |        |         |       |
| Samara factory          | 8.000       | 8.027  | 0.336  | 100.336 | 0.199 |
|                         | 16.000      | 16.031 | 0.193  | 100.193 | 0.025 |
|                         | 25.000      | 25.070 | 0.258  | 100.025 | 0.014 |
| Julpharlimited company  | 8.000       | 8.160  | 1.961  | 101.961 | 0.198 |
|                         | 16.000      | 16.040 | 0.249  | 100.249 | 0.025 |
|                         | 25.000      | 24.920 | -0.321 | 99.679  | 0.014 |
| Global limited company  | 8.000       | 8.040  | 0.498  | 100.498 | 0.199 |
|                         | 16.000      | 16.042 | 0.262  | 100.262 | 0.025 |
|                         | 25.000      | 24.960 | -0.160 | 99.84   | 0.014 |
| Ranbaxy limited company | 8.000       | 8.029  | 0.361  | 100.361 | 0.199 |
|                         | 16.000      | 16.020 | 0.125  | 100.125 | 0.025 |
|                         | 25.000      | 25.070 | 0.279  | 99.721  | 0.014 |

\* Average of five determinations

### Applicability of the proposed method

The proposed method was applied to determine of aspirin in pharmaceutical formulations purchased from local stores. The % recoveries of the studied drug compared with that obtained by the standard method are given in Table 4. The methods performance was assessed using the t-test for 95% confidence level with degree of freedom  $n_1+n_2-2=8$  and variance ratio F-value test for 95% confidence level with degree of freedom  $n-1=4$  compared with standard method. Statistical analysis of the results showed that calculated t- and F- values at 95% confidence levels are less than the theoretical ones, confirming no significant differences between the performance of the proposed and standard method in table-5.

Table 5: Comparison of the proposed method with standard method using t- and F- value

| No.                            | Standard method  |                     | Proposed method      |                     |               | Value             |                        |
|--------------------------------|------------------|---------------------|----------------------|---------------------|---------------|-------------------|------------------------|
| Origin of<br>Ranitidine tablet | Rec%*<br>Xi      | $(X_i - \bar{X})^2$ | Rec%*<br>$(X_i)_2^*$ | $(X_i - \bar{X})^2$ | S             | t-**              | F-**                   |
| Pure                           | 100.000          | 0.011               | 100                  | 0.053               | 0.058         | 0.8495<br>(2.306) | 0.966<br>(9.605)       |
| Samara factory                 | 99.700           | 0.038               | 99.913               | 0.001               |               |                   |                        |
| Global limited<br>company      | 99.925           | 0.001               | 99.683               | 0.157               |               |                   |                        |
| Julphar limited<br>company     | 100.225          | 0.1089              | 99.383               | 0.001               |               |                   |                        |
| Ranbaxy<br>limited<br>company  | 99.625           | 0.072               | 99.243               | 0.026               |               |                   |                        |
|                                | $\bar{X}=99.895$ | $\Sigma=0.231$      | $\bar{X}=99.644$     | $\Sigma=0.239$      | $n_1+n_2-2=8$ |                   | $n_1-1=4$<br>$n_2-1=4$ |

\* Average of five determinations, \*\* Theoretical t- and F- values at 95% confidence level 2.306 and 9.605, respectively

### Interference study

pharmaceutical analysis, it is important to test the selectivity towards the excipients added to the pharmaceutical preparations. Commonly encountered excipients such as glucose, lactose starch and Talcs did not interfere in the determination of Ranitidine. This gave an important advantage to the proposed pharmaceutical analysis, it is important to test the selectivity towards method.

### Conclusion

Despite the great number of methods described in the literature for analysis of Ranitidine-HCl, the proposed method for the determination of Ranitidine-HCl in pharmaceutical samples have the advantage to be simple, sensitive, accurate and inexpensive. The method represented good accuracy and precision so that the respective relative standard deviation and relative error of prediction for drug were lower. The proposed method was applied successfully to analysis of drugs in tablets and thus is very appropriate for routine quality control analysis of drug.

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