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Research Article

KINETIC ESTIMATION OF GABAPENTIN AND ETORICOXIB IN PHARMACEUTICALS

B. S. VIRUPAXAPPA*[1], K.H.SHIVAPRASAD[1]

Department of Chemistry, PG Centre, Bellary, Gulbarga University, Gulbarga, Karnataka, India
Email: virupaxb@gmail.com; ravirajmk@git.edu

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ABSTRACT

Kinetic spectrophotometric methods have been developed and validated for the determination of Analgesics drugs, Gabapentin and Etoricoxib in their pharmaceutical dosage forms. The method is based on the oxidation of Gabapentin and Etoricoxib with alkaline and acidic potassium permanganate respectively. In alkaline medium permanganate (Mn^{+7}) oxidizes Gabapentin and undergoes one electron reduction to give a green colored manganate ions (Mn^{+6}) which has wavelength maximum at 610 nm, and unreacted permanganate at 526 nm. In acidic medium the course of the reaction was conveniently followed by measuring the absorbance of permanganate at 526 nm, as the permanganate undergoes five electrons reduction to give divalent manganese ions (Mn^{+2}) . The calibration graphs for both drugs are linear in the concentration ranges from 17.2 – 86 µg/ml and 35.9 – 35 µg/ml for fixed time and rate constant methods respectively.

Keywords: Etoricoxib, Gabapentin, Kinetic spectrophotometry, Constant time method, Rate constant method.

INTRODUCTION

Gabapentin hydrochloride is chemically known as 1- (amino methyl) cyclohexane acetic acid hydrochloride. It is an intermediate product of Gabapentin which is a potent antiepileptic drug in adult patients who have not achieved adequate drugs control of partial seizures with these agents used alone or combination. It has a simple pharmacokinetic profile and is not protein bound. It is particularly useful in controlling secondarily generalized tonic- clonic seizures. The molecular formula of gabapentin hydrochloride is $C_9H_{18}ClNO_2$. The molecular weight of gabapentin hydrochloride is 207.70 with CAS Registry number 60142-96-3.Gabapentin Hydrochloride is used as an anticonvulsant [1, 2, 3]. It increases GABA in the brain and binds with voltage- sensitive Ca^{2+} channels. It also prevents neuronal death. For the determination of gabapentin hydrochloride, different analytical instruments such as High performance Liquid Chromatography (HPLC) [4-5], Liquid Chromatography – Mass Spectrophotometry (LC-MS) [6-7], Gas Chromatography – Mass spectrophotometry (GC-MS) [8], HPLC [9,10,11,12,13,14]. Gas chromatography- mass spectrometry [15, 16], capillary electrophoresis [17], Potentiometry [18], spectrofluorimetry [19] and spectrophotometry [20, 21].To the best of my knowledge, few attempts have been made to determine gabapentin by colorimetric method and the literature in this field is scanty.

Etoricoxib 5-chloro-2-[6-methylpyridine-3-yl]-3[4-sulfonylphenyl] pyridine) is a novel, selective second generation cyclo-oxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis [22-23]. It is an off-white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions [24]. Etoricoxib is available in tablet dosage forms (60, 90,120 mg) and is not official in any pharmacopoeia by official monograph of drug candidate [25]. The therapeutic importance of this drug has prompted the development of many methods for its assay. This drug is not officials in any pharmacopoeia. Several methods have been reported for the analysis of Etoricoxib in pharmaceutical dosage form as well as in the biological fluids and tissues, i.e. Spectrophotometric methods [26-27], chromatographic methods HPLC [28, 29, 30], LC/ Mass spectrophotometry [31, 32, 33, 34]. No Kinetic spectrophotometric methods were reported for the analysis of gabapentin and Etoricoxib, either in biological fluids and pharmaceutical formulations. This paper suggests simple and sensitive kinetic spectrophotometric procedures for the determination of gabapentin and Etoricoxib in pharmaceutical formulations. The chemical structure of Gabapentin and Etoricoxib is shown in (fig.1).

EXPERIMENTAL

Apparatus

A Peltier Accessory (Temperature controlled) Varian Cary 50 model UV-Vis spectrophotometer equipped with 1 cm quartz cell was used for all spectral measurements. Systronics pH meter were used for the accurate pH determinations.

Materials and reagents

All the materials were of analytical reagent grade, and the solutions were prepared with double distilled water, samples of Gabapentin and Etoricoxib were generously supplied by their respective manufactures and were used without further purification. The Gabapentin and Etoricoxib were procured as gift samples from (Vardhman Chemtech Ltd, Mohali, Punjab) & (Torrent Research center, Ahmedabad). Potassium permanganate (Merck, Germany) 1 x 10^{-3} M solution was prepared by dissolving 0.0395g $KMnO_4$ in 100 ml of double distilled water, followed by boiling and filtration through sintered glass. Potassium permanganate solution should be freshly prepared and its molarity was checked titrimetrically. Sodium hydroxide (Merck, Germany), 2M NaOH was prepared by dissolving 8g of NaOH in 100ml of double distilled water. 2 M perchloric acid was prepared by dissolving 17.5 ml of $HClO_4$ in 100 ml of double distilled water. 2M $NaClO_4$: was prepared by dissolving equal proportions of 2M NaOH and 2M $HClO_4$.

Preparations of standard solution

A Working standard solution of 0.01 M Gabapentin was prepared by dissolving .237 g in 100 ml of 0.1 N NaOH and Etoricoxib was prepared by dissolving in 0.359 g in 10% Acetic acid.

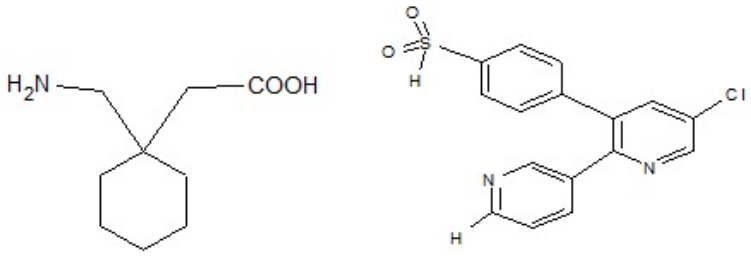
Kinetic procedure for antifungal drugs determination:

All kinetic measurements were performed under pseudo-first order conditions where Gabapentin and Etoricoxib used were at least 10 fold excess over permanganate at a constant ionic strength of 0.4 mol dm^{-3}.The reaction was initiated by mixing previously thermostatted solutions of $KMnO_4$ and analgesic drugs Gabapentin and Etoricoxib, which also contained the required quantities of $HClO_4$ and $NaClO_4$ to maintain the required acidity and ionic strength respectively. The temperature maintained at 25 ±0.1 ^oC. The course of the reaction was followed by monitoring the decrease in the absorbance of $KMnO_4$ at 526nm for both Gabapentin and Etoricoxib in alkaline and acidic medium respectively and also increase in the absorbance of manganate ion (Mn^{+6}) at 610nm was monitored for Gabapentin oxidation in alkaline medium.

RESULTS AND DISCUSSION

Potassium permanganate as strong oxidizing agent has been used in oxidimetric analytical method for determination of many compounds [35, 36, 37, 38]. During the course of the reaction, the valence of manganese changes from heptavalent manganese ion changes to the green color hexavalent manganese in alkaline medium, while in neutral and acid medium, the permanganate is reduced to color less divalent manganese. The behavior of permanganate was the basis for its uses in its development of spectrophotometric method. The absorption spectrum of aqueous potassium permanganate solution in alkaline medium exhibited an absorption band at 526 nm. The additions of any of the studied drugs to this solution produce a new characteristic banded 610 nm. This band is due to the formation of manganate ion, which resulted from the oxidation of analgesic drugs by potassium permanganate in alkaline medium. The intensity of the color increases with time; therefore a kinetically based method was developed for the determination of analgesic drugs in their pharmaceutical dosage formulations. The different variables that affect the formation of manganate ion were studied and optimized. Calibration graph of various kinetic procedures are given below.

The rate constant, constant concentration method and constant time methods were used for determining Gabapentin and Etoricoxib, and the best method was chosen based on applicability, the slope of the calibration graph, the intercept and the Correlation coefficient (r).



Gabapentin **Etoricoxib**

Fig.1 Structure of studied analgesic drugs

Initial rate method

The initial rate method was abandoned because, the graphs of the rate (at the beginning of the reaction) versus the drug concentration were not easy to obtain as the reaction was fast. Thus, the tangents to the curves at zero time were not easy to draw.

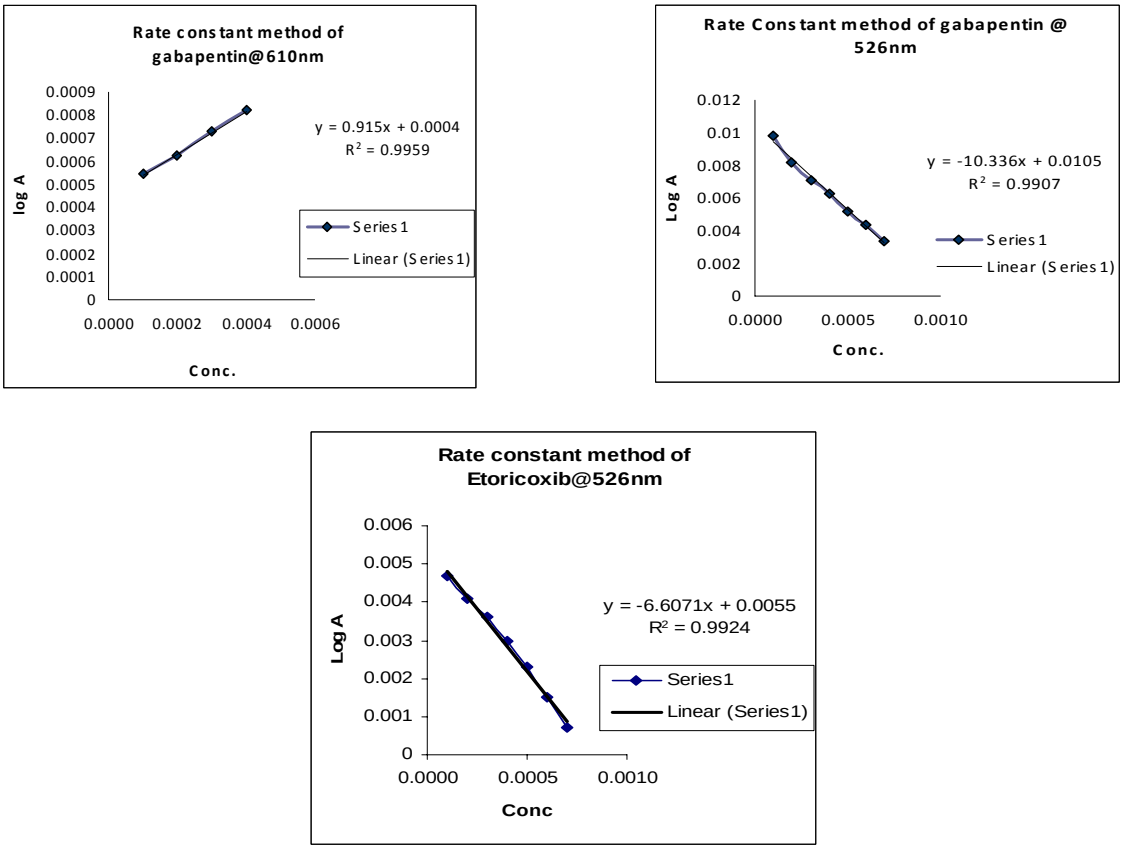


Fig. 2: calibration graph of gabapentin and etoricoxib for rate constant method

Rate constant method

In the rate constant method, Pseudo-first order rate constants were calculated for concentrations of Gabapentin and Etoricoxib in the range from 17.2 – 86 µg/ml and 35.9 – 251.3 µg/ml and are presented in (Table 1 & 2) respectively. A plot of K_{obs} versus [GABA and, ETR] is drawn, which was used as a calibration graph (Fig 2).

Constant concentration method

In constant concentration method, a preselected value of the absorbance was fixed and the time was measured for different drug concentrations (Table 2). The time versus the initial Concentration of drug was plotted, which could be used as a calibration graph.

The range of the drug concentrations giving the most acceptable calibration graph with the above was very limited which could be a disadvantage.

Constant time method

In constant time method, a pre-selected time (120secs) was fixed and the absorbance was measured for different concentrations of analgesic drugs (Table 1 & 2). A plot of the absorbance versus the initial concentration of analgesic drugs was drawn, which was linear and could be used as a calibration graph (Fig 3).

Table 1: Various kinetic methods for the determination of Gabapentin @ 610nm & 526nm in alkaline medium

[GABA]x 10^3/ mol dm^{-3}	Rate constant method K_{obs} x 10^3 / S^{-1}		Fixed concentration method(Abs = 0-15)		Fixed time method (t = 120 s) Abs.	
	610 nm	526 nm	610 nm	526 nm	610 nm	526 nm
0.1	5.48	9.8	250	90	2.08	5.97
0.2	6.22	8.2	200	80	2.16	5.86
0.3	7.27	7.1	160	70	2.26	5.79
0.4	8.18	6.3	110	50	2.34	5.55
0.5	9.04	5.2	080	40	2.48	5.42
0.6	10.21	4.4	050	30	2.61	5.29
0.7	11.39	3.3	-	-	2.76	5.11
0.8	12.13	3.0	-	-	2.91	4.87
0.9	13.21	2.2	-	-	3.06	4.74
1.0	14.19	-	-	-	3.18	4.55

Table 2: Various Kinetic methods for the determination of Etoricoxib nm @ 526 in acidic medium

[ETR]x10^3/ Method mol dm^{-3}	Fixed time (t = 120 s)	Fixed-concentration method(Abs = 0-15)	Rate constant Method K_{obs} x 10^3/S^{-1}
0.1	3.1	160	4.7
0.2	3.0	120	4.1
0.3	2.9	90	3.6
0.4	2.7	60	3.0
0.5	2.6	30	2.3
0.6	2.5	-	1.5
0.7	2.4	-	0.7
0.8	2.3	-	-
0.9	2.2	-	-
1.0	2.0	-	-

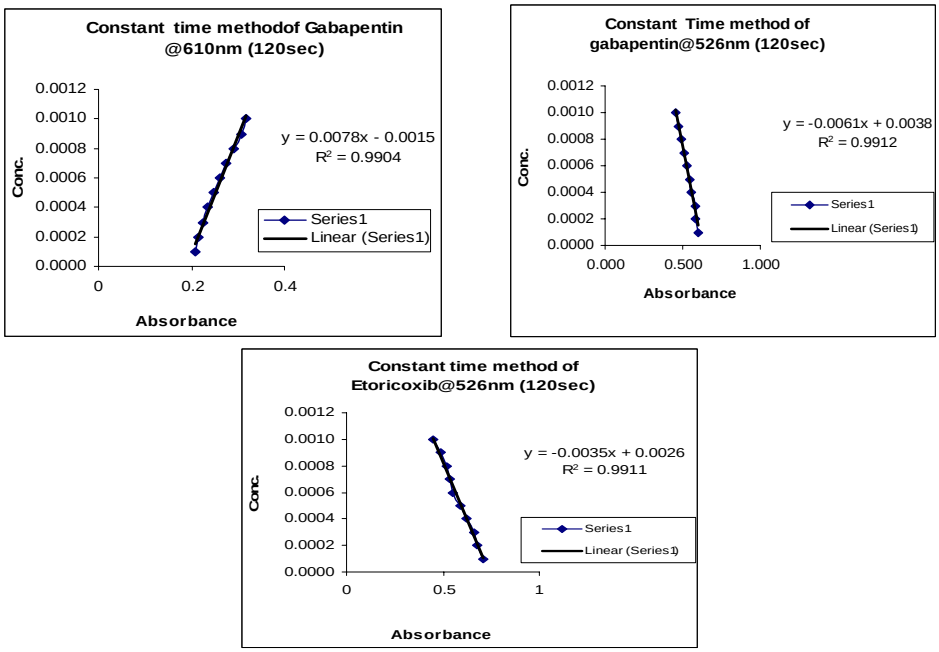


Fig. 3: Calibration graph of gabapentin & etoricoxib of constant time method

The range of the drug concentrations giving the most acceptable calibration graph with the above was 17.2- 172 µg/ml).

The best correlation coefficient was obtained for the Constant time method, and the value of the slope was also high. Even though the range was limited compared to the rate-constant method, the Constant-time method was found to be more applicable.

Application to pharmaceutical dosage forms

The calibration graph was used for the determination of drugs in pharmaceutical formulations. An accurately weighed amount equivalent to each 300 mg of Gabapentin drug from composite of 05 powdered tablets was transferred into a 100 ml volumetric flask. Dissolved in about 30 ml of acetone was added and the mixture was shaken for 5 min. The mixture was filtered using Whatman No. 42 filter paper and the filtrate was evaporated to dryness on a water bath. The residue was washed thoroughly several times with water before dissolving it in 0.1 N NaOH. The solution was then transferred into a 50 ml volumetric flask, made up to the mark with 0.1 N NaOH and suitable aliquot was then subjected to analysis using the procedure described under method 2.5 after diluting to 0 .01 M solution.

The contents of 10 capsules were evacuated and well mixed. Then an accurately weighed amount equivalent to 0.172 gm evacuated capsules of each drug transferred into a 100 mL beaker, and then the procedure was continued as described under tablets after diluting to 0.01 M Solutions.

An accurately weighed amount equivalent to each 250 mg of Etoricoxib drug from composite of 5 powdered tablets was transferred into a 100 ml volumetric flask. Dissolved in about 30 ml of acetone was added and the mixture was shaken for 5 min. The mixture was filtered using Whatman No. 42 filter paper and the filtrate was evaporated to dryness on a water bath. The residue was washed thoroughly several times with water before dissolving it in 10 % Acetic acid. The solution was then transferred into a 50 ml volumetric flask, made up to the mark with 10 % Acetic acid and suitable aliquot was then subjected to analysis using the procedure described under method 2.5 after diluting to 0 .01 M solution.

The vial is dissolved in 10 % Acetic acid and then the procedure was continued as described under tablets after diluting to 0.01 M Solution.

Validation of proposed methods

Statistical analysis of the results in comparison with the official method was done. The performance of the proposed method was judged by calculating the student t-test and variance ratio F-test. At the 95% confidence level, the calculated t- test and F-values do not exceed the theoretical values, indicating that there is no significant difference between the proposed method and the official method. From an analytical point of view, it is concluded that the described procedure allows for the determination of Analgesic drugs in pure and pharmaceutical dosage forms. Unlike the spectrofluorometer, as well as gas chromatographic and HPLC procedures, the instrument is simple and inexpensive. Its importance lies in the chemical reaction upon which the procedure is based, rather than sophistication of the instrument. This aspect of the kinetic method of determination is of major interest in analytical pharmacy, since it offers a distinct possibility for the assay of a particular component in complex dosage formulations.

Validation of the proposed method was done and concentration range is established by confirming that the analytical kinetic procedures provides a suitable degree of precision, accuracy and linearity when applied to the sample containing the amount of analyte within or at the extreme of the specified of the range of the analytical procedure. In this work,, concentrations ranging from 17.2 – 86 µg/ml & 35.9 – 251.3 µg/ml were studied for the investigated drugs in the Rate constant method and concentration ranging from 17.2 – 172 µg/ml & 35.9 - 359 µg/ml were studied for the investigated drugs in the constant time method (at preselected fixed time for 120 secs).The whole sets of experiments were carried out through this range to ensure the validation of the proposed procedure. Linear calibration graphs were obtained for all the studied drugs by plotting the logarithm of rate constant method of the reaction versus Absorbance of molar concentration of analyte in the sample within the specific range.

Precision was checked at three concentration levels. Eight replicate measurements were recorded at each concentration level. The calculated relative standard deviation were all below 2.2% indicating excellent precision of the proposed procedures at both level of repeatability and intermediate precision.

LOD was calculated based on standard deviation of response and the slope of calibration curve. The limit of detection was expressed as,

$$\mathrm{LOD} = \frac{3\sigma}{S}$$

Where σ is the standard deviation of intercept s is the slope of calibration curve. The results were summarized in (Tables 3 & 4) indicating good sensitivity of the proposed method .According to USP XXV guidelines, the calculated LOD values should be further validated by laboratory experiments. In our work, good results were obtained where the calculated by LOD equations were actually detected in these experiments.

Table 3: Analytical parameters of Gabapentin drug with alkaline $KMNO_4$

Drug/ Methods	Wave length	Linear Range(µg/ml)	Intercept	Correlation coefficient(R^2)	LOD	LOQ	Sandell's sensitivity
Gabapentin							
A. Rate	610	17.2 – 68.8	0.0005	0.9979	0.0198	0.0599	0.0000459
constant	526	17.2 - 86					
method			0.0105	0.9953	0.0028	0.0085	0.0004978
B. Constant time	610	17.2 - 172	0.1993	0.9921	0.0014	0.0043	0.0000143
method	526	17.2 – 154.8	0.6193	0.9944	0.0010	0.0031	0.0000061

Table 4: Analytical parameters of kinetic procedures for the determination of Etoricoxib drug with acidic $kmno_4$

Drug/ Methods	Linear range(µg/ml)	Intercept	Correlation coefficient(R^2)	LOD	LOQ	Sandell's sensitivity
Etoricoxib A.Rate constant method	35.9– 251.3	0.0055	0.9961	0.0754	0.0249	0.0010515
B.Constant time method	35.9 - 359	0.3267	0.9935	0.0023	0.00082	0.0000119

LOQ was calculated based on standard deviation of intercept and slope of calibration curve. In this method, the limit of quantization is expressed as

$$LOQ = 10\ \sigma\ S.$$

The results were summarized in (Table 3 and 4) indicating the good sensitivity of the proposed method. According to USP XXV guidelines, the calculated LOQ values should be further validated by laboratory experiments. In our work, good results were obtained where the calculated by LOQ equations were actually quantities in these experiments.

The Constant time method and rate constant methods of the proposed kinetic spectrophotometric method for the investigated drugs have been tested on commercial pharmaceutical dosage forms. The concentration of investigated drugs was computed from its responding regression equations. The results of proposed method (Constant time and rate constant methods) were statistically compared with those of reported methods, in respect to accuracy and precision. The obtained mean recovery values were recorded in (Table 5), which ensures that there is no interference of other additives present in the studied formulations.

In the t- and F- tests, no significant differences were found between the calculated (Table 5), and theoretical values of both the proposed and the reported methods at 95% confidence level. This indicates good precision and accuracy in the analysis of investigated Antifungal drugs in dosage forms.

CONCLUSION

The Constant time and rate constant methods can be easily applied for determination of investigated analgesic drugs in pure and dosage forms that do not require elaborate treatment and tedious extraction of chromophore produced. The proposed methods (Constant time & rate constant method) are sensitive enough to enable determination of lower amount of drugs. These advantages encourage the application of proposed method in routine quality control of examined analgesic drugs in industrial laboratories. Finally, our methods provides advantage of improving selectivity, avoiding interference of colored and or are turbidity background of samples because it measures the increase in absorbance with time against blank treated similarly.

Table 5: Analysis of Gabapentin & Etoricoxib in pharmaceutical formulations (Found values[a] ± SD% and comparison with the official method)

Drug	Labeled	Found (X ± SD) Proposed method	Reference method
Gabapentin			
Goben	300 mg/ Tab	298 ± 0.71 t = 0.32, F = 1.39	300.98 ± 0.43
Mygaba	300 mg/ Tab	296 ± 0.65 t = 0.42, F = 1.09	299.98 ± 0.13
Noegaba	300 mg/ Tab	297 ± 0.74 t = 0.82, F = 0.39	301.98 ± 0.23
Gabantin	100 mg/ Cap	98 ± 2.3 mg	99.5 ± 0.97 mg
Gabata	400mg/ Cap	t = 0.22, F = 2.01 398 ± 1.9 mg	397.2 ± 1.01 mg
Gaby	300mg/ Cap	t = 0.25, F = 1.99 208 ± 2.5 mg t = 0.5, F = 2.19	398.2 ± 1.27 mg
Etoricoxib			
1.Elenton	90 mg/ Tab	87 ± 0.78 t = 0.12, F = 0.59	90.2 ± 0.22 mg
2.Etobus	120 mg/ Tab	19 ± 0.48 t = 0.92, F = 1.49	122.2 ± 0.22 mg
3.Etoby	60 mg/ Tab	58 ± 0.34 t = 1.2, F = 0.93	62.21 ± 0.56 mg
Nucoxia	90 mg / ml/ Inj	89.21 ± 1.12 t = 0.2, F = 1.9	90.34 ± 0.21

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