

## Titrimetric, spectrophotometric and kinetic methods for the assay of atenolol using bromate–bromide and methyl orange

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**Abstract:** Three new methods have been developed for the determination of atenolol in bulk drug and in tablet formulation. The methods are based on the oxidation–bromination reaction of the drug by bromine, generated *in situ* by the action of acid on a bromate–bromide mixture. In the titrimetric method, the drug is treated with a known excess of bromate–bromide mixture in hydrochloric acid medium, followed by the determination of the unreacted bromine iodometrically. The spectrophotometric method involves the addition of a measured excess of bromate–bromide reagent in hydrochloric acid medium to atenolol, and after ensuring the reaction had gone to completion, the unreacted bromine is treated with a fixed amount of methyl orange, and absorbance measured at 520 nm. The absorbance was found to increase linearly with increasing concentration of atenolol. The kinetic method depends on the existence of a linear relationship between the concentration of the drug and the time of the oxidation–bromination reaction, as indicated by the bleaching of methyl orange acid colour. The working conditions were optimized. The titrimetric method is based on a 1:1 reaction stoichiometry (atenolol:bromate) and is applicable over the 3–20 mg range. The spectrophotometric method permits micro determination of the drug ( $0.5\text{--}4.0\ \mu\text{g ml}^{-1}$ ) with an apparent molar absorptivity of  $4.13 \times 10^4\ \text{l mol}^{-1}\ \text{cm}^{-1}$  and detection limit of  $0.07\ \mu\text{g ml}^{-1}$ . The kinetic method is applicable in the concentration range  $5\text{--}25\ \mu\text{g ml}^{-1}$  with a detection limit of  $3.72\ \mu\text{g ml}^{-1}$ . The proposed methods were successfully applied to the determination of atenolol in tablet preparations with mean recoveries of 97.63 to 101.78 %. The reliability of the assay was established by parallel determination by the reference method and by recovery studies using the standard addition technique.

**Keywords:** atenolol, determination, titrimetry, spectrophotometry, kinetics, bromate–bromide reagent, methyl orange, tablets.

### INTRODUCTION

The dosification and/or adulteration of commercially available pharmaceutical preparations demand the use of reliable methods for drug determination, which

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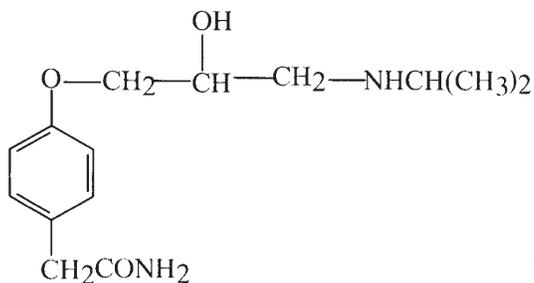


Fig. 1. Structure of atenolol.

are preferably selective, rapid and can be performed with simple equipment. This is true of atenolol, 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamide (Fig. 1), which in therapeutics is known as a beta-blocker and is widely used in the management of hypertension, angina pectoris, cardiac dysrhythmias and myocardial infarction.<sup>1</sup> The drug is official in the Indian Pharmacopoeia,<sup>2</sup> which describes a UV-spectrophotometric method for its assay in tablets. The drug is also official in the British Pharmacopoeia, which describes high-performance liquid chromatographic (HPLC) methods of assay, which are two-stage processes.<sup>3</sup> A wide range of chromatographic techniques, such as HPLC,<sup>4-13</sup> liquid chromatography,<sup>14-16</sup> thin layer chromatography,<sup>17</sup> gas-liquid chromatography<sup>18,19</sup> and non-suppressed ion chromatography,<sup>20</sup> have been used to determine atenolol. Sensitive methods based on the measurement of the self-fluorescence exhibited by atenolol in 0.1 M hydrochloric acid and phosphate-borate buffer have been described.<sup>21,22</sup> Other techniques include UV-spectrophotometry,<sup>23-30</sup> kinetic spectrophotometry,<sup>31</sup> differential scanning calorimetry and thermogravimetry,<sup>32</sup> electrophoresis<sup>33-35</sup> and nuclear magnetic resonance spectroscopy.<sup>36,37</sup> Many of the reported methods<sup>4-13,21,22</sup> are sensitive but require expensive instruments. Although HPLC methods with UV and fluorescence detection are routinely used, these methods require complicated liquid-liquid or liquid-solid extraction steps and/or several complicated clean-up steps.<sup>4-13</sup> They are time consuming and often poorly reproducible. The kinetic method<sup>31</sup> is less sensitive and involves a heating step, whereas the thermal methods<sup>32</sup> require expensive experimental setup, in addition to being poorly sensitive. Recently, chemometric<sup>33</sup> and chemometric-assisted spectrophotometric<sup>34</sup> methods have been proposed for the assay of atenolol in combined dosage forms.

Titrimetry and visible spectrophotometry are well established techniques which when applied to pharmaceutical products, can be considered to be the methods of choice owing to their selectivity, reduced implementation costs and versatility of application. There is only one report on the titrimetric<sup>35</sup> determination of atenolol, but it requires 200 mg of drug for each determination for accurate results. The majority of the reported visible spectrophotometric methods<sup>36-40</sup> lack the sensitivity and simplicity required of routine analysis. The determination of the drug based on the reaction with hydroxylamine and iron(III) chloride in acid medium forming the reddish-violet ferric hydroxamate complex<sup>36</sup> has been reported, but

the molar absorptivity is too low ( $\epsilon = 570$ ) and the procedure involves boiling for 20–30 min. The colorimetric method reported by Zakhari *et al.*,<sup>37</sup> based on the reaction of the drug with copper(I) and carbon disulphide involves multiple extraction steps, in addition to being poorly sensitive (linear range, 8–56  $\mu\text{g ml}^{-1}$ ). The other colorimetric method,<sup>38</sup> based on the reaction of atenolol with acetaldehyde and halogenated benzoquinones, also involves an extraction step and the use of an organic solvent as diluent. The method using haematoxylin as reagent<sup>39</sup> is also poorly sensitive. The recently reported<sup>40</sup> ion-pair extraction spectrophotometric methods, with the use of two dyes, Wool Fast Blue and Trapaeolin 000, also lack sensitivity ( $\epsilon = 623$ ). Hitherto, no work based on a redox/substitution reaction for the determination of atenolol has been undertaken. This paper reports three methods based on the oxidation–bromination of atenolol by bromine (generated *in situ* by the action of acid on bromate–bromide reagent) followed by the determination of the excess bromine by iodometric titration or by the bleaching of the acid colour of methyl orange. The methods are simple, rapid and sensitive and can be conveniently used in laboratories where modern expensive instrument such as that required for fluorimetry, electrophoresis, GLC or HPLC is not available.

## EXPERIMENTAL

### Apparatus

A systronics Model 106 digital spectrophotometer provided with matched 1-cm quartz cells was used for all absorbance measurements.

### Reagents

All employed chemicals were of analytical grade, and all solutions were freshly prepared in distilled water.

*Bromate–bromide mixture (0.01 M KBrO<sub>3</sub>–0.05 M KBr)*. Prepared by dissolving 1.67 g of KBrO<sub>3</sub> (Sarabhai M. Chemicals, Baroda, India) and 2.38 g of KBr (Qualigens Fine Chem, Mumbai, India) in water and diluting to 1 liter with water and used in the titrimetric and kinetic methods. The mixture was appropriately diluted with water to obtain 10  $\mu\text{g ml}^{-1}$  KBrO<sub>3</sub> containing a 5-fold molar excess of KBr.

*Methyl orange (50  $\mu\text{g ml}^{-1}$ )*. A 1000  $\mu\text{g ml}^{-1}$  stock solution was prepared by dissolving 52.4 mg of the dye (S. d. Fine Chem., India; dye content 85 %) in water and diluting to 100 ml in a volumetric flask, and filtered through glass wool. The filtrate was appropriately diluted to obtain a 50  $\mu\text{g ml}^{-1}$  dye solution for use in spectrophotometry. Fifty ml of the above stock solution (1000  $\mu\text{g ml}^{-1}$ ) was diluted to 1 liter after the addition of sufficient sulphuric acid to maintain an overall acid concentration of 1 M, for use in the kinetic method.

*Sodium thiosulphate (0.06 M)*. The solution was prepared by dissolving 14.89 g of the chemical (Sisco. Chem Ind. Mumbai, India) in water and diluting to 1 liter with water.

*Potassium iodide (10 %)*. Prepared by dissolving 10 g of the chemical (Qualigens Fine Chem, Mumbai, India) in 100 ml of water.

*Starch Indicator (1 %)*. About 1 g of soluble starch (S.d. Fine Chem., Mumbai, India) was dropped into 100 ml of boiling water, and cooled.

*Hydrochloric acid (5 M)*. Prepared by diluting 443 ml of concentrated acid (Qualigens Fine Chem. Mumbai, India) Sp. Gr. 1.18 to 1 liter with water.

*Standard solution of atenolol (2 mg ml<sup>-1</sup>)*. Pharmaceutical grade atenolol (0.5 g) (supplied by Cipla India Ltd., Mumbai, India, as a gift) was dissolved in water and made up to volume in a 250 ml

volumetric flask. The solution was diluted stepwise with water to obtain working concentrations of 10 and 100  $\mu\text{g ml}^{-1}$  for use in the spectrophotometric and kinetic method, respectively.

#### Procedures

**Titrimetry.** A 10 ml aliquot of a drug solution containing 3–20 mg of atenolol was accurately measured into a 100 ml iodine flask and acidified by adding 4 ml of 5 M hydrochloric acid. Then, 10 ml of 0.01 M  $\text{KBrO}_3$  – 0.05 M KBr mixture was added by means of a pipette, the flask was stoppered, the contents were mixed well and left to stand for 15 min with occasional swirling. Finally, 5 ml of 10 % potassium iodide solution was added and the liberated iodine titrated with 0.06 M thiosulphate to a starch end point. A blank experiment was repeated without atenolol. The amount of atenolol in the aliquot was calculated from the amount of bromate consumed.

**Spectrophotometry.** Different aliquots, 0.5–4.0 ml of 10  $\mu\text{g ml}^{-1}$  atenolol solution were transferred into separate 10 ml volumetric flasks by means of a micro burette and the total volume was maintained at 4 ml by adding water. Two ml of 5 M hydrochloric acid were added to each flask followed by 1 ml of bromate–bromide reagent (10  $\mu\text{g ml}^{-1}$  with respect to  $\text{KBrO}_3$ ). The flasks were stoppered, the contents were mixed well and the flasks were set aside for 10 min with occasional shaking. Finally, 1 ml of 50  $\mu\text{g ml}^{-1}$  methyl orange solution was added to each flask, diluted to the mark with water and mixed well. The absorbance of each solution was measured at 520 nm against a reagent blank after 5 min. The concentration of the unknown was read from the calibration graph or calculated using the regression equation obtained by using the Beer law.

**Kinetic analysis.** Different aliquots, 5–25 ml of 100  $\mu\text{g ml}^{-1}$  atenolol solution were accurately transferred into separate 50 ml volumetric flasks each containing 25 ml of methyl orange solution (50  $\mu\text{g ml}^{-1}$  in 1 M sulphuric acid). Into separate test tubes of similar dimensions, 5.0 ml each of the above drug solutions and 0.01 M bromate – 0.05 M bromide mixture were pipetted out. The tubes were immersed in an ice bath until they reached 4–5 °C. A stop-clock was started and the two solutions were mixed in one of the tubes noting the time of addition (Initial time,  $T_i$ ). The mixture was stirred while kept in the ice bath with the help of the thermometer used for the temperature measurement. The time required for the bleaching of the methyl orange colour was noted (Final time,  $T_f$ ). The actual time was given by  $T_e = T_f - T_i$ . A blank experiment was carried out simultaneously by mixing the bromate–bromide mixture with the methyl orange solution, without the addition of atenolol, and the time required to bleach the acid colour of the dye was noted ( $T_b$ ). The corrected time,  $T_c = T_e - T_b$  was computed. A calibration curve was prepared by plotting the corrected time,  $T_c$  as a function of the atenolol concentration or the regression equation was obtained using the same data. The concentration of the unknown was read from the calibration graph or calculated using the regression equation.

## RESULTS AND DISCUSSION

Preliminary experiments revealed that atenolol is prone to both oxidation and substitution reaction by bromine generated, *in situ* by the action of acid on a bromate–bromide mixture. In the titrimetric method, the reaction was followed by back titration of the unreacted bromine iodometrically, while in the spectrophotometric method, it was followed by measuring the increase in the absorbance of the methyl orange acid colour at 520 nm, the change in absorbance being caused by bleaching action of bromine. The same bleaching action was used to follow the oxidation–bromination reaction kinetically.

#### Optimisation of the reaction conditions

**Titrimetry.** The quantitative nature of the reaction between atenolol and bromine was checked by treating 3–20 mg of drug with a known excess of bromate

te-bromide reagent in acid medium and back titrating the surplus bromine iodometrically. The stoichiometry was calculated to be 1:1 (drug:  $\text{KBrO}_3$ ).

The reaction was carried out in hydrochloric acid medium. The reaction stoichiometry was found to be unaffected when 2–9 ml of 5 M acid was used in a total volume of about 30 ml. The reaction was found to have gone to completion after 15 min and contact times up to 60 min had no effect on the stoichiometry. For the studied range (3–20 mg), 10 ml of 0.01 M bromate – 0.05 M bromide reagent was found to be adequate for completion of the reaction and a two-fold increase in the bromate concentration had no effect on the stoichiometry of the reaction.

*Spectrophotometry.* Many acid dyes are prone to oxidation to form colourless products in acid medium thus offering a suitable analytical approach for the indirect assay of oxidisable pharmaceuticals<sup>41–49</sup> using various oxidizing agents, including the bromate–bromide reagent.<sup>46–49</sup> Gyory<sup>50</sup> used methyl orange as the indicator in the direct titration with bromate–bromide solution, the drug being irreversibly bleached at the end point. In the proposed spectrophotometric method using methyl orange, different amounts of atenolol were treated with a fixed excess of bromate–bromide reagent in hydrochloric acid medium and the unreacted bromine was determined by treating with a fixed amount of the dye and measuring the increase in absorbance at 520 nm. The increase in absorbance was found to be directly proportional to the atenolol concentration.

The experimental conditions for the assay were optimized. One ml of  $50 \mu\text{g ml}^{-1}$  methyl orange acid form in a total volume of 10 ml gave a convenient absorbance. This colour was completely and irreversibly bleached by 1 ml of  $10 \mu\text{g ml}^{-1}$   $\text{KBrO}_3$  in the presence of a large excess of bromide. Hence, different amounts of atenolol were reacted with 1 ml bromate–bromide reagent ( $10 \mu\text{g ml}^{-1}$  w.r.t  $\text{KBrO}_3$ ), and after the oxidation–bromination reaction was judged to be complete, the surplus bromine was determined by treating with 1 ml of methyl orange solution and measuring the absorbance at 520 nm, to determine the range of applicability.

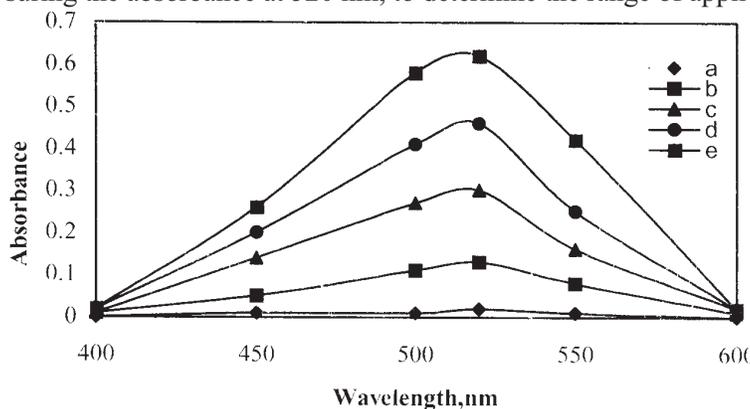


Fig. 2. Absorption spectra of: a. Reagent Blank; b, c, d and e are after treatment with 10, 20, 30 and 40  $\mu\text{g}$  of atenolol.

Atenolol when added in increasing amounts, consumes bromine and consequently there will be a concomitant decrease in the bromine concentration. This

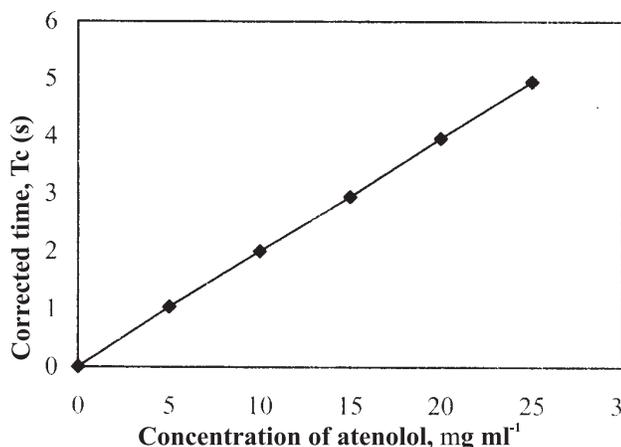


Fig. 3. Calibration curve for atenolol.

was observed as a proportional increase in the absorbance at 520 nm when treated with a fixed amount of methyl orange (Fig. 2). An overall acidity of 0.5 M with respect to hydrochloric acid, which was used for the oxidation–bromination reaction was also maintained for the bleaching action. Acidity up to 1.5 M produced the same results. The oxidation–bromination reaction was complete after 10 min for 0.5–4.0  $\mu\text{g ml}^{-1}$  range of drug concentration and a contact time of 5 min was found necessary for the bleaching action. The measured absorbance of the methyl orange acid colour was found to be stable for up to one day.

*Kinetic method.* The bleaching action of bromine on methyl orange has been successfully utilized for the kinetic determination of organic pharmaceuticals, such as albendazole,<sup>46</sup> famatodine,<sup>47</sup> salbutamol sulphate,<sup>48</sup> propranolol,<sup>49</sup> paracetamol,<sup>50</sup> stilbestrol,<sup>51</sup> phenylephrine hydrochloride,<sup>52</sup> salicylamide and tetracline hydrochloride<sup>53</sup> and ascorbic acid.<sup>54</sup> In the proposed method for atenolol, different amounts of atenolol were mixed with a fixed amount of methyl orange and made 0.5 M with respect to sulphuric acid. Equal volumes of the drug–dye solution and 0.01 M  $\text{KBrO}_3$  M 0.05 KBr solution, each at 4–5 °C, were mixed and the time for required the red colour of methyl orange to be discharged was measured and corrected for the blank experiment. When increasing amounts of atenolol were reacted with a fixed amount of bromate–bromide, the concentration of the latter decreased concomitantly after the oxidation–bromination reaction. This resulted in an increase in the time required for the bleaching of a fixed amount of methyl orange. This is observed as a proportional increase in the corrected time ( $T_c$ ) with increasing amounts of atenolol (Fig. 3). A linear relationship was found between the corrected time and the concentration of atenolol, which formed the basis for the quantification of the drug.

#### Analytical data

Titrimetry was found to be applicable over the range 3–20 mg. Outside these limits, deviant inconsistent were obtained. The relationship between the titration end point and the amount of drug was evaluated by calculating correlation coeffi-

cient,  $r$ , via the linear least square method, and was found to be  $-0.9968$ , suggesting that the reaction between atenolol and bromate proceeds stoichiometrically in the ratio 1:1.

In the spectrophotometric method, the Beer law was obeyed over the concentration range,  $0.5\text{--}4.0 \mu\text{g ml}^{-1}$ . The apparent molar absorptivity and the Sandell sensitivity were  $4.13 \times 10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$  and  $6.44 \text{ ng cm}^{-2}$ , respectively. The linear plot gave the regression equation:

$$A = 0.001 + 0.155 c (r = 0.9993; n = 8)$$

where  $A$  is the absorbance and  $c$  the concentration in  $\mu\text{g ml}^{-1}$ . The detection and quantification limits were calculated from the standard deviation of the absorbance measurements obtained from a series of seven blank solutions. The limit of detection ( $K = 3$ ) and the limit of quantification ( $K = 10$ ) were established according to the IUPAC definitions<sup>55</sup> and were found to be  $0.07$  and  $0.24 \mu\text{g ml}^{-1}$ , respectively.

The calibration graph for the kinetic method was obtained by plotting the corrected time ( $T_c$ ) in seconds against the atenolol concentration and linearity was found in the range  $5\text{--}25 \mu\text{g ml}^{-1}$  and can be described by the equation:

$$T_c = 0.03 + 0.19 c (r = 0.9998; n = 5)$$

where  $T_c$  is the corrected time in seconds and  $c$  the concentration in  $\mu\text{g ml}^{-1}$ . The limits of detection and quantification were calculated to be  $3.72$  and  $12.40 \mu\text{g ml}^{-1}$ , respectively.

#### *Accuracy and precision of the methods*

To evaluate the accuracy and precision of the proposed methods, pure drug at three different levels was determined, each measurement being repeated seven times. The results obtained from this study are summarized in Table I. The titrimetric and spectrophotometric methods are fairly accurate and precise as revealed by the relative error ( $< 2\%$ ) and the relative standard deviation ( $< 3\%$ ). The kinetic method was found to be relatively less accurate and precise. The reproducibility on a day-to-day basis, was estimated by analyzing the standard drug solution at three levels on five consecutive days. In terms of standard deviation, the day-to-day coefficient of variation was less than  $3\%$  for the titrimetric and spectrophotometric methods and around  $5\%$  for the kinetic method.

TABLE I. Evaluation of the accuracy and precision of the proposed methods

Titrimetric				Spectrophotometric				Kinetic			
Amount taken mg	Amount found* mg	Relative Error %	RSD %	Amount taken $\mu\text{g}$	Amount found* $\mu\text{g}$	Relative Error %	RSD %	Amount taken $\mu\text{g}$	Amount found* $\mu\text{g}$	Relative Error %	RSD %
5.00	4.89	2.20	2.86	1.00	1.02	2.00	2.94	10.00	9.82	1.80	3.22
10.00	10.12	1.20	2.38	2.00	1.98	1.00	1.97	15.00	14.78	1.46	1.65
15.00	14.86	0.93	2.57	3.00	3.04	1.33	2.63	20.00	20.26	1.30	2.71

\*Mean value of seven determinations; RSD – Relative standard deviation

*Application to tablet analysis*

In order to demonstrate the applicability of the proposed methods to the assay of atenolol in preparations, four brands of commercially available tablets were analysed for the active ingredient by the proposed methods. The results of the assay summarised in Table II reveal good agreement between the declared content and percent found. The results obtained by the proposed methods were compared with those obtained by the reference method<sup>2</sup> by applying the Student's *t*- and *F*- tests at the 95 % confidence level. The calculated *t*- and *F*- values did not exceed the tabulated values (*t* = 2.77, *F* = 6.39) for four degrees of freedom suggesting that there was no significant difference between two of the proposed methods and the reference method in terms of accuracy and precision. However, the kinetic method is not as accurate and precise as the reference method.

TABLE II. Results of the assay of tablets by the proposed methods

Tablet brand name*	Nominal value/mg	Titrimetry	Spectrophotometry	Kinetic	Official method
Aten <sup>a</sup>	100	97.96 ± 0.85	98.64 ± 1.26	99.14 ± 1.88	98.76 ± 0.62
		<i>t</i> = 1.72	<i>t</i> = 0.20	<i>t</i> = 1.20	
		<i>F</i> = 1.88	<i>F</i> = 4.13	<i>F</i> = 9.19	
Atecard <sup>b</sup>	100	101.23 ± 1.02	101.36 ± 0.94	100.78 ± 1.64	100.62 ± 0.96
		<i>t</i> = 0.97	<i>t</i> = 1.18	<i>t</i> = 1.41	
		<i>F</i> = 1.13	<i>F</i> = 4.18	<i>F</i> = 2.92	
Betacard <sup>c</sup>	50	99.35 ± 1.24	100.16 ± 1.28	97.63 ± 1.66	98.78 ± 0.86
		<i>t</i> = 0.86	<i>t</i> = 2.04	<i>t</i> = 1.44	
		<i>F</i> = 2.07	<i>F</i> = 2.21	<i>F</i> = 9.57	
Telol <sup>d</sup>	50	98.26 ± 1.67	98.74 ± 0.42	99.10 ± 2.86	97.56 ± 1.28
		<i>t</i> = 0.75	<i>t</i> = 1.01	<i>t</i> = 1.17	
		<i>F</i> = 1.70	<i>F</i> = 3.57	<i>F</i> = 4.99	

\*Marketed by a: Korpan Limited; b: Dabour Pharmaceutical Ltd.; c: Torrent Pharmaceuticals; d: Max India Ltd.; Calculated *t* value at 95 % confidence level was 2.77; Calculated *F* value at 95 % confidence level was 6.39

The accuracy and validity of the methods were further ascertained by performing recovery studies *via* the standard addition technique. When a tablet powder (pre-analysed) spiked with known amounts of pure drug was analysed, the recoveries of the added pure drug were quantitative (Table III) revealing that common additives and excipients, such as talc, starch, gumacacia, lactose, sodium alginate, magnesium stearate, calcium gluconate, calcium dihydrogen orthophosphate, did not interfere in the determination.

TABLE III. Results of the recovery study by the standard addition method

Preparation studies	Titrimetric			Spectrophotometric				Kinetic				
	Amount of drug in tablet mg	Amount of pure drug added mg	Total found mg	Recovery of pure drug %	Amount of drug in tablet µg	Amount of pure drug added µg	Total found µg	Recovery of pure drug %	Amount of drug in tablet µg	Amount of pure drug added µg	Total found µg	Recovery of pure drug %
Aten (100 mg)	4.03	4.0	8.12	102.25	9.96	10.0	20.24	102.80	49.94	100.00	154.12	104.18
	4.03	8.0	11.95	99.00	9.96	20.0	29.49	97.66	49.94	150.00	196.06	99.41
	4.03	12.0	16.39	103.00	9.96	30.0	39.72	99.20	49.94	200.00	249.26	99.64
Atecard (100 mg)	4.95	4.0	8.94	99.75	9.92	10.0	19.93	100.08	50.02	100.00	153.33	102321
	4.95	8.0	13.21	103.25	9.92	20.0	30.17	101.26	50.02	150.00	201.14	100.68
	4.95	12.0	16.77	98.50	9.92	30.0	39.76	99.48	50.02	200.00	247.14	98.56
Total (100 mg)	6.04	4.0	9.96	98.00	10.02	10.0	20.35	103.26	49.92	100.00	152.20	102.28
	6.04	8.0	14.22	102.25	10.02	20.0	30.02	100.00	49.92	150.00	199.11	99.46
	6.04	12.0	18.54	104.17	10.02	30.0	39.49	98.23	49.92	200.00	245.90	97.99

\*Mean value of three determinations

## CONCLUSIONS

The assay results demonstrate that it is possible to use a bromate–bromide solution as an oxidimetric and brominating agent for the determination of atenolol in authentic samples. The methods allow the determination of amounts as small as 5  $\mu\text{g}$  and as large as 20 mg of atenolol with a fair degree of accuracy and precision. The methods developed can be rapidly carried out, are simple to perform, and do not require specific sample treatments. The titrimetric method is the first ever developed on the basis of a redox/substitution reaction, and is more sensitive than the only other titrimetric method<sup>35</sup> found in the literature, which requires 200 mg for each determination. The spectrophotometric method for the determination of atenolol is also easier and cheaper to perform than many currently available methods<sup>4–37</sup> and is 10 to 100-fold more sensitive than the existing spectrophotometric methods.<sup>36–40</sup> Even the kinetic method is much more sensitive than most of the procedures known, but is not very precise. The procedures are suitable for the analysis of atenolol in pharmaceuticals, as there are no interferences from the excipients normally found in commercial formulations.

## ИЗВОД

ТИТРИМЕТРИЈСКА, СПЕКТРОФОТОМЕТРИЈСКА И КИНЕТИЧКА МЕТОДА  
ЗА ОДРЕЂИВАЊЕ АТЕНОЛОЛА УЗ КОРИШЋЕЊЕ БРОМАТ–БРОМИДА И  
МЕТИЛ-ОРАНЖА

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Предложене су методе за одређивање атенолола како у узорцима сировине тако у таблетама. Одређивање је засновано на реакцији бромовања при чему реагује бром настао реакцијом бромат–бромиде *in situ*. У титриметријској методи одређује се вишак неизреагованог брома, а у спектрофотометријској вишак брома се третира дефинисаном количином метил-оранжа и мери апсорбанција на  $\lambda = 520 \text{ nm}$ . Кинетичка метода се заснива на линеарном односу концентрације лека и времена реакције оксидације–бромовања. Оптимизовани су радни услови и одређене границе детекције атенолола. Методе су примењене на одређивање атенолола у таблетама са задовољавајућим процентом приноса од 97,63 – 101,79 %.

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